Summary of Research Activities by Disease Category

Neuroscience and Disorders of the Nervous System

Often viewed as the last biological frontier, the brain is perhaps the most intriguing organ in the human body. For centuries, efforts to understand the human brain ultimately have yielded to its inaccessibility, protected by the skull and invisible to X-rays; and to its complexity, with some 100 billion interconnected neurons. Yet, over just the last few decades, major advances in noninvasive brain imaging technologies have allowed researchers and clinicians to peer inside the living, working human brain. Such sophisticated neuroimaging techniques have become invaluable research tools, revealing structural and functional changes in nervous system disorders that point to their causes and that could aid in their diagnosis and treatment. In 2009, the NIH Blueprint for Neuroscience Research launched a bold new initiative to apply these cutting-edge technologies to a long-held grand challenge in neuroscience: mapping the connectivity of the entire living human brain. The Human Connectome Project will combine the use of multiple brain imaging methods with demographic and genetic data, as well as information on sensory, motor, cognitive, emotional, and social function, in hundreds of healthy adults. Neuroimaging already has improved clinical outcomes in important ways by, for example, identifying stroke patients likely to benefit from the clot-busting drug tPA and guiding neurosurgery and device implantation. Brain imaging also has been used experimentally in conjunction with neurofeedback training, in which patients learn to control pain perception, and a similar approach might one day help substance abusers control drug cravings. The Human Connectome Project will build on and accelerate such advances, and may yield unprecedented insights into fundamental questions in neuroscience that rest on understanding the connections between brain areas and how they are altered in disorders such as autism, schizophrenia, and epilepsy.

Introduction

Composed of the brain, spinal cord, and nerves of the body, the nervous system underlies perception, movement, emotions, learning and memory, and other functions essential to individual and societal well-being. The nervous system interacts with all other organ systems and is affected by countless diseases, conditions, and environmental factors. Moreover, with limited capacity for self-repair, the nervous system is particularly vulnerable to damage due to injury or infection, and its repair mechanisms are poorly understood. Neuroscience research seeks to understand the nervous system and its functions in health and disease. Given its intrinsic complexity and central role in physiology and behavior, this understanding must necessarily come from multiple perspectives. Accordingly, neuroscience research spans many disciplines, from genetics to physiology to psychology, and applies tools from areas such as molecular biology, anatomy, computer sciences, and imaging technologies.

Neuroscience is a unifying theme in NIH research. The intramural and extramural programs of several ICs have a major focus on the nervous system, but the full scope of neuroscience activities extends to components of research portfolios across most of NIH, reflecting the multidisciplinary nature of the field and the importance of the nervous system to many aspects of human health, development, and disease. These activities often involve collaborative efforts combining the unique strengths and expertise of individual ICs, and to reinforce such collaborations, NIH established the Blueprint for Neuroscience Research.[11] The Blueprint accelerates neuroscience research through training programs, the development of shared tools and resources, and initiatives to address challenges in neuroscience that transcend the mission of any single IC.

The principal aim of NIH research in neuroscience is to reduce the burden of diseases that affect the nervous system, including a broad range of neurological disorders; disorders affecting cognitive, emotional, and behavioral function; diseases and conditions that impair the primary senses; and developmental and age-related disorders. Whether led by single investigators or conducted through centers and consortia, NIH neuroscience research includes basic science studies of normal function and development in both humans and animal models, translational research that develops medications or other therapies, and clinical trials that test interventions in patients.

Nervous system disorders include common killers and major causes of disability like stroke, multiple sclerosis, and epilepsy, as well as hundreds of less common diseases, such as lysosomal storage disorders, spinal muscular atrophy, muscular dystrophies, inherited neuropathies, neurofibromatosis, tuberous sclerosis, and Rett and Tourette syndromes. Many neurological disorders have genetic or developmental origins. Others result from trauma to the nerves, spinal cord, or brain; from autoimmune, infectious, or systemic disease; from tumor growth in nervous system tissues (also see the section on *Cancer* in Chapter 2); or from neurodegenerative processes as in Parkinson's disease, frontotemporal dementia, and amyotrophic lateral sclerosis (ALS). NIH research on neurological diseases, largely supported by NINDS, seeks to uncover their causes and mechanisms and to develop drugs and other treatments or preventive strategies. This research also aims to understand the multiple aspects of the nervous system that disease can affect and has shared support across NIH for basic science studies of the cerebral vasculature, electrochemical signaling in neurons and other cells, mechanisms of development and cell death, neuromuscular function and motor control, and behavior and cognition. In addition, NIH works to enhance the lives of those disabled by stroke, traumatic brain injury, spinal cord injury, and other neurological conditions through research supported by NICHD's National Center for Medical Rehabilitation Research and other ICs on neuroplasticity, recovery and repair of motor and cognitive function, and rehabilitative and assistive strategies and devices (also see the section on *Life Stages, Human Development, and Rehabilitation* in Chapter 2).

Brain disorders affecting cognitive, emotional, and behavioral function include schizophrenia and psychoses; autism spectrum disorder and other developmental disorders; mood and anxiety disorders; addiction to nicotine, alcohol, and other substances; and post-traumatic stress disorder, eating disorders, attention deficit hyperactivity disorder, and other behavioral disorders. These disorders have complex causes involving genetic and environmental influences and their interactions throughout life. Through research efforts led by NIAAA, NIDA, NIMH, and other ICs, NIH focuses on uncovering these causes, understanding their neural and behavioral bases, and developing therapies and interventions for treatment and prevention. NIH research also seeks to understand the acute and long-term effects of abused substances on the nervous system.

Sight, smell, balance, and our other primary senses, as well as the ability to communicate, allow interactions with a changing external environment. NEI and NIDCD sponsor most of NIH's research on basic mechanisms of sensory perception and communication and on diseases and conditions affecting the eyes and vision, hearing and balance, voice, speech and language, taste and smell, and somatosensory function, including the senses of temperature and touch. Although vital to survival, the sensation of pain also is symptomatic of many diseases with origins in and outside the nervous system, from migraine and other headaches to cancer-related pain conditions. NIH pain research is led by NIDCR and the NIH Pain Consortium, which coordinates research across NIH on pain and its treatment (also see the section on *Chronic Diseases and Organ Systems* in Chapter 2). NIH-supported research also studies the many ways the nervous system interacts with and regulates changes in the body's internal environment. This research, including efforts supported by NHLBI and NIDDK, focuses on areas such as circadian rhythms and sleep disorders; neuroendocrine processes that regulate stress responses, hormone levels, and motivational states; and the neural basis of appetite and feeding, which is of key relevance to slowing the increasing rates of obesity worldwide.

Nervous system disorders may arise in development, strike young adults, or emerge late in life. NICHD and other ICs sponsor research on the development of the nervous system and its functions. This research encompasses studies of structural birth defects, including spina bifida and other neural tube defects and associated conditions such as hydrocephalus. NIH also invests in research on developmental disorders like cerebral palsy, Down syndrome, autism spectrum disorder, and other causes of intellectual and learning disabilities. Nervous system development continues into early adulthood in humans, and developmental processes and their external influences contribute to mental fitness and disease risk later in life, including the risk for addiction, which often begins in childhood or adolescence. At the other end of the lifespan, with key support from NIA, NIH research on the aging nervous system includes studies of age-related disorders such as Alzheimer's disease and other dementias, as well as environmental and lifestyle factors affecting neurological, cognitive, and emotional health in aging populations.

Across all ages, the nervous system is a common target of exposure to toxins, pollutants, and other agents, whose effects range from acute reactions to developmental disorders and neurodegeneration. NIH-sponsored research on the consequences of such environmental exposures for nervous system function and disease includes a particular focus by NIEHS. NIH also considers diseases of the nervous system from a global point of view. Coordinated primarily by FIC, NIH supports neuroscience-related research around the world in unique populations and environments and on factors contributing to disparities in disease vulnerability and treatment quality and access, such as socioeconomic conditions and infectious disease.

[11] Institutes and Centers participating in the NIH Blueprint for Neuroscience Research: NEI, NIA, NIAAA, NIBIB, NCCAM, NICHD, NCRR, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR, and OBSSR.

Burden of Illness and Related Health Statistics

Nervous system disorders take an enormous toll on human health and the economy. Even rare disorders carry a substantial collective burden, as they often have an early onset and long duration, and the stigma commonly attached to neurological and mental illnesses further compounds individual and societal impact. According to 2005 estimates, neurological disorders strike more than 1 billion people worldwide, account for 12 percent of total deaths, and result in more disability than HIV/AIDS, ischemic heart disease, or malignant tumors.[12] In the United States, stroke is the third leading killer of adults and results in annual medical and disability costs totaling nearly $70 billion.[13] Each year, another 1.4 million Americans sustain traumatic brain injury (TBI), the leading cause of death and long-term disability in young adults,[14] with direct and indirect costs reaching approximately $60 billion in 2000.[15] Head injury also accounts for an estimated 20 percent of combat-related injuries in modern wars, and blasts are a leading cause of TBI in military personnel.[16]

In a given year, approximately 12.5 million American adults (or 1 in every 17) suffer a debilitating mental illness.[17,18] Mental disorders result in more disability for U.S. adults than any other class of medical illness,[19] and a conservative estimate places the total direct and indirect annual costs of mental illness at more than $300 billion.[20] In 2008, among persons in the United States ages 12 years or older, 18.3 million were classified with dependence on or abuse of alcohol, and 7.0 million were classified with dependence on or abuse of illicit drugs.[21] The overall social and economic burden of substance abuse continues to rise, with annual costs related to alcohol and illicit drug abuse totaling $235 billion[22] and $181 billion,[23] respectively.

Mental illness and neurological disorders affect people of all ages. An estimated 17 percent of U.S. children have a developmental or behavioral disorder such as autism spectrum disorder, intellectual

disability, or attention deficit hyperactivity disorder.[24] Current demographic trends project a growing burden from age-related diseases of the nervous system as populations benefit from increased longevity. One in 7 U.S. adults ages 72 years and older has dementia, and estimates of the prevalence of Alzheimer's disease range from 2.4 million to 5.1 million, a number expected to rise to as many as 13.2 million by 2050 unless effective interventions are developed.[25,26]

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NIH Funding for Neuroscience and Disorders of the Nervous System

Actual NIH funding support levels for research in neuroscience and disorders of the nervous system were $5,224 million in FY 2008, and $5,320 million and $848 million in FY 2009, respectively, for non-ARRA (regular appropriations) and ARRA (Recovery Act appropriations). Click on the funding levels, which are live links, to produce detailed project listings. These lists are derived from the NIH Research, Condition, and Disease Categorization (RCDC) system. In addition, the table at the end of this chapter indicates some of the research areas involved in this investment (see *Estimates of Funding for Various Research, Condition, and Disease Categories*).

Summary of NIH Activities

Neurodevelopment, neuroplasticity, and neurodegeneration are common themes that reflect shared biological processes found in many aspects of nervous system function and disease. In this section, these themes will serve to highlight selected examples of activities and progress in neuroscience research enabled by NIH, as well as challenges and future opportunities. Additional activities and initiatives exemplify how collaborative approaches are facilitating advances in basic, translational, and clinical neuroscience. More information, as well as more examples, can be found in the bulleted list at

the end of this section.

Neurodevelopment: Periods of Growth, Maturation, and Vulnerability

Complex interactions between gene expression and function, endocrine and other physiological processes, neuronal activity, and external influences guide the development of the nervous system. From the early differentiation of its many neuronal and other cell types to the establishment of billions of synapses, or connections between neurons, each step in nervous system development is vulnerable to disruption by disease, injury, or environmental exposures. NIH research across all stages of neurodevelopment is leading to a better understanding of neurological, mental, and behavioral function in health and disease throughout life, as well as to new treatments and preventive strategies.

During early human embryonic development, a flat surface of cells destined to become the brain and spinal cord rolls into a structure called the neural tube. Defects resulting from improper neural tube formation, including spina bifida and anencephaly, are among the most common birth defects. Sufficient dietary folic acid before conception and during early pregnancy can reduce the risk of neural tube defects, but although the United States and other countries now fortify their food supplies with folic acid, not all neural tube defects are prevented, indicating that other risk factors also may contribute. NIH-supported research recently conducted in collaboration with investigators in Ireland showed an elevated risk for neural tube defects in children born to mothers with low blood levels of vitamin B12 shortly before and after conception. This research suggests that, in addition to folic acid, women expecting to conceive may be able to further reduce the risk of neural tube defects by consuming sufficient amounts of vitamin B12.

Recent NIH-supported research also provided strong evidence for an inexpensive and easily prescribed treatment to prevent cerebral palsy in children born prematurely. Cerebral palsy refers to a group of nonprogressive neurological disorders that result from damage to the developing fetal or infant brain, leading to abnormal control of movement and posture. Early preterm birth is a major risk factor for cerebral palsy and is associated with approximately one-third of all cases. NIH supported the largest, most comprehensive effort to date to determine whether magnesium sulfate, a drug routinely given to prevent seizures in women with preeclampsia and to delay preterm labor, could protect against the risk for cerebral palsy when given to pregnant women likely to give birth prematurely. The randomized, controlled clinical trial showed that severe or moderate cerebral palsy occurred significantly less frequently after treatment with magnesium sulfate as compared to placebo.

Both genetic and environmental factors influence nervous system development and function, and a growing area of neuroscience research focuses on how genes and the environment interact in a range of disorders including multiple sclerosis, Parkinson's disease, depression and other mood and anxiety disorders, addiction, and autism spectrum disorders. As part of the NIH Collaborative Study on the Genetics of Alcoholism (COGA), a longitudinal study during adolescence—a stage of life marked by increased susceptibility to alcohol use disorders—has identified several genes associated with the risk for alcoholism and related behaviors such as anxiety, depression, and other types of drug dependence. Other NIH-supported studies focus on how environmental influences, such as parenting quality, exposure to abused drugs, socioeconomic status, and neighborhood characteristics, affect brain development and behavior, contributing to the goal of understanding the role of these factors in drug abuse initiation.

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NIH supports broad efforts to understand how autism spectrum disorders (ASD) may arise from combined effects of genetic vulnerabilities and exposure to potentially harmful environmental agents during key periods of development. As one example, the Early Autism Risk Longitudinal Investigation (EARLI) is following a cohort of 1,200 mothers who have children diagnosed with ASD through a subsequent pregnancy (also see the section on Autism Centers of Excellence in Chapter 4). This study will help determine the contribution of environmental factors, such as in utero exposure to organic pollutants, to ASD risk in families that already may be genetically susceptible to the disorder. Although all forms of ASD are characterized by challenges in three core domains of functioning (social impairments; communication difficulties; and restricted, repetitive, or stereotyped patterns of behavior), considerable heterogeneity exists across individuals with ASD in these and other clinical features, suggesting the contribution of multiple developmental trajectories and causal factors. One cross-cutting theme highlighted in the Interagency Autism Coordinating Committee (IACC) Strategic Plan for ASD Research is the need to understand this heterogeneity, which could lead to new insights into the causes of ASD, improved diagnosis, and more targeted intervention strategies. To address this need, NIH issued a series of funding opportunity announcements titled, "Research to Address the Heterogeneity in Autism Spectrum Disorders," for research on ASD measurement, biomarkers and biological signatures, immune and central nervous systems interactions, genetics and genomics, environmental risk factors, and intervention and treatment. Funds from the American Reinvestment and Recovery Act of 2009 will support this collaborative effort among several NIH ICs, the largest single funding opportunity for ASD research in NIH history. NIH intends to use additional ARRA funds to jumpstart many of the short-term objectives of the IACC Strategic Plan, through the Challenge Grants in Health and Science Research Program (RFA-OD-09-003), and Grand Opportunity grants (RFA-OD-09-004).

The human brain continues to mature into early adulthood, and understanding normal nervous system development is essential to knowing when, where, and how developmental processes can go wrong. In the NIH Magnetic Resonance Imaging (MRI) Study of Normal Brain Development, NIH-supported researchers at 7 collaborating institutions collected brain scans and clinical and behavioral data from more than 500 healthy infants, children, and adolescents over the course of 7 years, providing important baseline information that could identify signs of atypical brain development. The data gathered and analytical tools developed for this longitudinal study are available to the broader research community in a Web-based, searchable database. An improved understanding of the normal course of human brain development also is yielding insights into behavioral and cognitive development and function across the lifespan. For example, previous brain imaging studies have shown that one of the last brain areas to fully mature is the prefrontal cortex, an area important for decision-making and impulse control. This aspect of brain development may contribute to impulsive behavior in teenagers and help explain their increased susceptibility to drug abuse and addiction. NIH-supported research also recently has shown a delay of about 3 years in the development of the prefrontal cortex in children with attention-deficit/hyperactivity disorder (ADHD) as compared to age-matched children without the disorder.

NIH investigators already are using knowledge about human brain and behavioral development to guide research on interventions to treat nervous system disorders or to reduce their risk of occurrence later in life. For example, researchers reporting delayed development of the prefrontal cortex in ADHD now are studying the effects of ADHD treatment on the rate of cortical maturation. To reduce the incidence of substance abuse disorders in children and adolescents, NIH supports evidence-based research to target an array of risk factors and behaviors through developmentally appropriate preventive strategies, including interactive Web-based programs and encouraging physical activity as a way to counter drug use. The NIH Underage Drinking Initiative similarly supports research on underage drinking and its risk factors, as well as efforts to develop and implement

effective interventions, all within a developmental framework.

Neuroplasticity: Substrates for Change and Repair

Throughout development, and even once its basic structure and circuitry have been established, the nervous system retains a remarkable capacity to adapt to changes in the body's internal environment and external conditions and events. This capacity, known as plasticity, alters the function and activity of neuronal networks, and it occurs at many levels of the nervous system, from altered signaling at synapses thought to underlie learning and memory, to large-scale functional and neuroanatomical reorganization accompanying the loss of a limb or sensory organ. Plasticity enables beneficial adaptations, including acquiring new knowledge, improving performance, and adjusting behavior. However, it also can lead to maladaptive changes, and neuroplasticity-related mechanisms contribute to a range of disorders, including mood disorders, addiction, chronic pain, and obesity. By better understanding these mechanisms, researchers may be able to both harness their therapeutic potential and limit their deleterious consequences.

Mood disorders, such as depression and anxiety, are associated with changes in the function of brain networks involved in emotion, and treatments targeting plasticity mechanisms could alleviate these disorders and reduce their recurrence. NIH researchers previously demonstrated that low doses of ketamine—an anesthetic that blocks brain receptors known to be involved in neuroplasticity—can act as a rapid antidepressant, lifting symptoms within hours, while conventional medications take weeks. Further research now has identified changes in brain activity in depressed patients that correlated with their responsiveness to ketamine's rapid antidepressant effects, and that therefore may reflect brain network changes underlying their depression. NIH also supports research on treatments for mood disorders through clinical trial networks. Ongoing studies include the Lithium Use for Bipolar Disorder (LiTMUS) trial and the Combining Medications to Enhance Depression Outcomes (CO-MED) trial, which will examine for the first time whether two different medications, when given in combination as the first treatment step, will enhance remission and provide better sustained benefits than treatment with a single medication. Other NIH support for research on mood disorders includes a new program for Innovative Approaches to Personalizing the Treatment of Depression.

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Neuroplasticity underlies a range of changes in brain function and behavior involved in the development and persistence of addiction. In particular, the same brain mechanisms mediating reward-related learning also contribute directly to addiction. NIH-supported investigators recently mapped the genomic effects of chronic cocaine use in the reward center of the mouse brain using a powerful new technique known as ChIP-chip, which can identify epigenetic changes, or lasting changes in gene expression caused by mechanisms other than alterations in the underlying DNA sequence. Such analyses of the genetic and epigenetic effects of cocaine and other abused substances may point to new targets for intervention. Stress-related systems in the brain also contribute to addiction and relapse. NIH researchers have investigated specific brain chemicals that mediate behavioral stress responses for their contributions to alcohol dependence, and they are building on their insights to develop new treatments. In one study, alcohol-dependent patients who recently had stopped drinking were treated with a drug that blocks signaling through the receptor for a stress-related molecule called neurokinin 1. The treatment reduced alcohol cravings, improved overall well-being, and reduced blood levels of stress hormones. It also altered brain activity in ways that suggested a potential for reducing the likelihood of relapse in alcohol-dependent individuals. As a promising alternative for treating addiction, NIH also supports the development of vaccines for drug

addiction, an approach called immunotherapy. Unlike conventional small molecule therapy, which acts on neural signaling pathways involved in drug addiction, in immunotherapy, a vaccine targets the drug itself. The vaccine stimulates the production of drug-specific antibodies, which bind the drug in the blood and prevent its entry into the brain. This diminishes or completely blocks the drug's reinforcing effects on addiction-related neural signaling, and therefore may lead to reduced drug use. In a recent Phase II clinical trial, a vaccine developed against nicotine showed strong positive results in promoting abstinence among study participants who achieved sufficient antibody levels. Other innovative treatment approaches under development with NIH support include medications to promote new learning and diminish conditioned responses to drug-related cues, which may help counter cravings or alter expectations of reward associated with drug use.

In a recent Phase II clinical trial, a vaccine developed against nicotine showed strong positive results.

Plasticity also is an important factor in the development and persistence of pain disorders. Opioid analgesics are the most powerful medications currently available to treat chronic pain, but they can unfortunately result in addiction, tolerance, and physical dependence, limiting their value in some patients. One focus of NIH-supported research to develop new treatments is the cannabinoid signaling system. Just as the brain produces natural opioid-like compounds, it also produces natural compounds that act on the same receptors as the neuroactive component in the cannabis plant (marijuana). Cannabinoid signaling modulates neuronal activity and plasticity and also plays a role in modulating pain. Research suggests that selective activation of cannabinoid signaling pathways may provide analgesia with minimal psychotropic effects. NIH-supported researchers also have reported new findings on the mechanisms that lead to neuropathic pain induced by nerve injury. Most available treatments for neuropathic pain target neurons. In contrast, the new findings highlight the role of certain enzymes released by non-neuronal cells called glia, which are involved in immune and inflammatory responses to nerve injury. Future treatments targeting glia may provide a way to halt the maladaptive signaling cascade that results in neuropathic pain. NIH also supports efforts to exploit adaptive plasticity at the level of brain networks for therapeutic pain intervention. Using real-time brain imaging, researchers have shown that patients with chronic pain can learn to exert voluntary control over activation of a particular brain region involved in pain perception and its regulation, effectively reducing the impact of their painful sensations.

Although plasticity can lead to changes in neural activity patterns throughout life, the adult human brain and spinal cord have a limited capacity to actually replace or repair neurons that are lost or damaged by injury or disease. An exciting area of neuroscience research focuses on ways to overcome these limitations to promote recovery and restore function. For example, spinal cord injury often leads to permanent paralysis and loss of sensation below the site of injury because damaged nerve fibers are unable to regrow across the injury site. NIH supports research to understand the mechanisms that restrict such regrowth and to design strategies that integrate new nerve fibers into spinal circuitry. In one study, researchers showed in a mouse model of spinal cord injury that self-assembling nanofibers reduced scar formation and cell death, promoted regeneration of nerve fibers across the injury site, and improved functional recovery. As another example, researchers long thought the adult human brain could not generate new neurons. However, more current research has shown that the production of neural stem cells—which can become new neurons or other types of brain cells—continues into adulthood in certain brain regions. NIH supports research on the role of these cells in normal function, injury, and disease, as well as on the potential for treatments that tap into this intrinsic renewal mechanism. The results of a recent study suggest that stem cells isolated from the adult brain may be able to replace lost sound-detecting cells in the inner ear, providing a foundation for future treatments of hearing loss.

Neurodegeneration: Fighting the Effects of Age, Exposure, and Disease

The progressive loss of neurons is a common endpoint of many diseases and insults to the nervous system. Such degeneration presents challenges to developing strategies to slow and prevent cell death, protect remaining neurons, and possibly replenish those that are lost. Recent and ongoing NIH research on neurodegenerative diseases focuses on understanding their biological and environmental causes and on efforts to develop interventions that not only alleviate their symptoms, but that may slow or even stop disease progression.

Alzheimer's disease is the most common cause of dementia in the elderly, though some inherited forms of the disease become symptomatic in middle age. Scientists now believe that damage to the brain begins well before symptoms appear. NIH-supported basic research on Alzheimer's disease mechanisms has contributed in recent years to industry development of new drug treatments. NIH also supports translational research efforts to move basic research findings toward clinical applications. A recent study reported that a grape seed-derived extract reduced Alzheimer's disease-like neuropathology and cognitive decline in a mouse model, indicating promise for further therapeutic development of this extract, which is likely to be safe and well-tolerated in people. In addition, NIH supports clinical trials for treating and slowing Alzheimer's disease, many of which are coordinated through the Alzheimer's Disease Cooperative Study (ADCS), involving nearly 70 sites in the United States and Canada. In 2009, five new clinical trials were underway through the ADCS. One study will examine the clinical utility of intravenous immunoglobulin, which contains naturally occurring antibodies targeting beta amyloid, a protein implicated in Alzheimer's disease. Other studies include a multicenter trial to evaluate home-based assessment methods for Alzheimer's disease prevention research, and trials to test treatment with the omega-3 fatty acid DHA, the anticonvulsant drug valproate, and an oral compound formulated to prevent beta amyloid from binding to a specific brain receptor.

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NIH actively is engaged in identifying gaps in Parkinson's disease research and developing programs to address them. Examples of progress include initiation of Phase III clinical trials of creatine and coenzyme Q10 to treat early Parkinson's disease; development of diagnostic criteria for depression and psychosis in people with Parkinson's disease; and support for a Parkinson's disease Gene Therapy Study Group. In 2009, a major clinical trial co-funded by NIH and the Department of Veterans Affairs published its finding that deep brain stimulation is more effective than standard drug therapy for Parkinson's disease but also carries higher risk of adverse events. NIH also supports 14 Morris K. Udall Centers for Excellence in Parkinson's Disease, which are identifying and characterizing disease-associated genes, examining neurobiological mechanisms, improving Parkinson's disease animal models, and developing and testing potential therapeutics. Three NIH Centers for Neurodegeneration Science also conduct research on Parkinson's disease. These centers will focus on gene-environment interactions, biomarkers to help identify people at risk, and mechanisms that may link exposure to toxic chemicals, such as agricultural pesticides, to increased susceptibility for Parkinson's disease.

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Aging is the most consistent risk factor for developing a neurodegenerative disorder, and many of the

50 million adults in the United States 60 years and older are at substantial risk for cognitive impairment and emotional disorders from many causes as they age. In addition, age-related cognitive decline distinct from dementia will affect most older individuals to some extent, with direct impacts on their independence and vitality. Although cognitive training, physical exercise, enhanced self-efficacy, social engagement, diet, environmental enrichment, and stress reduction all have been shown to have positive effects on cognition, the quality of the evidence varies widely across studies. NIH is partnering with the McKnight Brain Research Foundation through the Foundation for NIH to support the initial development and pilot testing of behavioral interventions that, individually and in combination, may remediate age-related cognitive decline.

Hearing and visual impairments also can result from degenerative processes. Tinnitus, the perception of ringing, roaring, clicking, or hissing sounds in the ears in the absence of an actual external sound source, is generally associated with age-related or noise-induced hearing loss. The neural basis of tinnitus remains poorly understood, and an NIH-supported study used brain imaging techniques for the first time in a rat model of tinnitus to identify brain regions affected by the condition. In other NIH-supported research, a recent examination of data from the National Health and Nutrition Examination Survey (NHANES) showed that hearing loss is about twice as common in adults with diabetes compared to those who do not have the disease. Diabetes may lead to hearing loss by damaging the nerves and blood vessels of the inner ear, disrupting blood flow to the inner ear, which is essential for normal hearing. NIH also supports research to develop interventions to treat or prevent degenerative sensory impairments, such as efforts to protect against optic nerve damage associated with glaucoma, a major cause of blindness. Researchers recently showed in a mouse model of glaucoma that overexpressing the gene for a naturally occurring neuroprotective factor improved survival of neurons in the retina that make up the optic nerve.

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Neurons are not unique in their vulnerability to degenerative disorders. Muscular dystrophies are a class of neuromuscular disorders that lead to progressive muscle weakness and degeneration. NIH support for research on muscular dystrophies includes funding for six Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (also see the section on *Wellstone Muscular Dystrophy Cooperative Research Centers* in Chapter 4), as well as targeted initiatives for translational research in neuromuscular disease. Multiple sclerosis is the most common of a number of diseases that lead to the degeneration of myelin, a fatty substance that ensheathes many nerve fibers in the brain. In 2007, a genome-wide association study with NIH support reported the first new genetic risk factors for multiple sclerosis to be identified in more than 20 years, and in 2009, meta-analyses and replication studies revealed additional new susceptibility genes. NIH also supports an ongoing randomized, double-blind, placebo-controlled Phase III trial (CombiRx) comparing the efficacy of treatment combining beta-interferon and glatiramer acetate vs. treatment with either agent alone for relapsing-remitting multiple sclerosis. The trial will determine whether combination therapy offers an improvement over the partial efficacy of either of these commonly used medications. NIH intramural investigators are collaborating with this trial to identify biomarkers associated with different clinical and treatment response profiles.

Advancing Neuroscience Research through Collaboration

The melding of disciplines involved in the study of the nervous system and the overarching themes linking its many functions and disorders make neuroscience a naturally collaborative field of research.

The NIH Blueprint for Neuroscience Research, a trans-NIH collaboration among 16 NIH ICs and Offices, catalyzes research progress by developing tools, research resources, and training opportunities that transcend the mission of any single NIH IC and serve the entire neuroscience community. Looking forward, the NIH Blueprint plans to support initiatives addressing Grand Challenges in the areas of pain research, mapping human brain connectivity, and therapy development for diseases of the nervous system. Further examples of collaboration in neuroscience research range from other joint activities across NIH ICs and Federal agencies, to data sharing and multisite networks in the research community, to coordinated efforts between NIH, extramural researchers, and those directly affected by disease to identify research needs and opportunities.

Looking forward, the NIH Blueprint for Neuroscience Research plans to support initiatives addressing Grand Challenges in the areas of pain research, mapping human brain connectivity, and therapy development for diseases of the nervous system.

Today's fast global communication, the power and storage capacity of modern computer systems, and advanced informatics tools are enabling collaborative research on increasingly large scales. NIH supports several data registries, databases, and tissue banks for neurological diseases and mental disorders that offer shared access to research resources, genetic and clinical data, and biological samples. For example, the National Database for Autism Research (NDAR)) is a collaborative biomedical informatics system created by NIH to house human genetic, imaging, and phenotypic data from research on ASD, and to make these data available to qualified researchers. In addition, through community-based development of a data dictionary, NDAR will foster a shared, common understanding of the complex data landscape that characterizes ASD research. The Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC), a NIH Blueprint program, provides information about and access to research tools and resources for the neuroimaging research community. In 2009, the NITRC received the "best overall" Excellence.gov award, the largest Federal award program to recognize the very best in government information technology programs. (Also see the section on *Disease Registries, Databases, and Biomedical Information Systems* in Chapter 3.)

NIH also facilitates collaborative approaches to research on disorders of the nervous system through many clinical and translational research networks and other programs that enable multisite studies. The Alzheimer's Disease Neuroimaging Initiative (ADNI), NIH's largest public-private partnership for brain research, is examining the potential for serial magnetic resonance imaging, positron emission tomography, or other biomarkers to measure earlier, and with greater sensitivity, the development and progression of mild cognitive impairment and Alzheimer's disease. A recent ADNI study confirmed that changes in cerebrospinal fluid biomarkers may signal the onset of mild Alzheimer's disease and established a method and standard of testing for these biomarkers. The Specialized Program of Translational Research in Acute Stroke (SPOTRIAS) supports a network of eight research centers established to develop acute stroke therapies from preclinical research through early-phase clinical trials. These centers also work to improve pre-hospital stroke care, participate in community education, and develop telemedicine to expand rapid access to acute stroke care. Additional NIH programs facilitate research on rare disorders, which would not be possible without a coordinated effort. For example, in 2009, NIH established the Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC), a network of more than 200 community and academic practitioners for the study of risk factors, diagnosis, and treatments for neuro-ophthalmologic disorders such as idiopathic intracranial hypertension and ocular manifestations of Grave's disease, an autoimmune disorder. Several consortia funded through the NIH Rare Diseases Clinical Research Network (also see the section on *Rare Diseases Clinical Research Network* in Chapter 4) program focus on neurological disorders, including dystonia, brain vascular malformations, lysosomal storage disorders, and rare diseases of the autonomic nervous system.

The Alzheimer's Disease Neuroimaging Initiative, NIH's largest public-private partnership for brain

research, is examining the potential for serial magnetic resonance imaging, positron emission tomography, or other biomarkers to measure earlier, and with greater sensitivity, the development and progression of mild cognitive impairment and Alzheimer's disease.

NIH intramural investigators have worked with the Department of Defense (DOD) and the Department of Veterans Affairs (VA) for many years on long-term neuropsychological outcomes of traumatic brain injury (TBI) in veterans. The high rate of TBI and post-traumatic stress disorder (PTSD) among military personnel returning from ongoing operations in Afghanistan and Iraq has led to expanded and new joint efforts with these and other agencies. Recent trans-agency workshops have focused on TBI classification, combination therapies for TBI, research opportunities and challenges for blast injury-induced TBI, and common data elements related to TBI and PTSD. In an ongoing collaborative effort with the DOD Centers of Excellence and the VA to address the role of gender, race, and other socioeconomic factors on trauma spectrum disorders, NIH also has helped define directions for new interdisciplinary studies on the prevention, diagnosis, treatment, and management of TBI and PTSD, including a focus on their impact on families and communities and on increasing knowledge about women with TBI and PTSD.[27] In addition, the Center for Neuroscience and Regenerative Medicine (CNRM) is a newly established collaboration between the Uniformed Services University of the Health Sciences (USHUS) and the NIH Intramural Research Program for research on TBI. Projects within the center range from molecular and mechanistic studies to rehabilitation and outcomes research.

To identify research needs and opportunities, NIH relies strongly on the advice of the extramural research community, as well as on the important perspectives of people directly affected by disease. The NIH Epilepsy Research Benchmarks represent one of many examples of such collaborative activities across neuroscience to determine priority areas for research. The Benchmarks, first developed in 2000 and revised in 2007, reflect input from epilepsy researchers, physicians, patients, family members, and nonprofit organizations that support the epilepsy community and research efforts. NIH continues to collaborate with the broader epilepsy community to address the Benchmarks, including through a recent workshop on sudden unexplained or unexpected death in epilepsy (SUDEP), which focused on research needs to understand and prevent SUDEP, and on improving awareness and education about SUDEP for patients, families, and health care providers.

[27] For more information, see http://www.nih.gov/news/health/sep2008/od-15.htm.

Notable Examples of NIH Activity

Key
E = Supported through **E**xtramural research I = Supported through **I**ntramural research O = **O**ther (e.g., policy, planning, or communication) COE = Supported via congressionally mandated **C**enter **o**f **E**xcellence program GPRA Goal = **G**overnment **P**erformance and **R**esults **A**ct ARRA = **A**merican **R**ecovery and **R**einvestment **A**ct IC acronyms in **bold** face indicate lead IC(s).

Neurodevelopment: Periods of Growth, Maturation, and Vulnerability

Developmental Genomics: Neural tube defects are a class of birth defects affecting the brain and spinal cord. Taking folic acid during the weeks before and after conception greatly can reduce a woman's chances of having a child with a neural tube defect. Still, researchers have not yet fully defined the complex relationship that exists between folic acid and vitamin B12, which is essential for synthesizing DNA during growth and development. Because Ireland has a particularly high rate of neural tube defects, NIH researchers collaborated with Irish researchers to look more closely at the role of vitamin B12 in the developmental disorder. They found that children born to women who have low blood levels of vitamin B12 shortly before and after conception have an increased risk of a neural tube defect. In light of their discovery, researchers said it would be wise for all women of childbearing age to consume the recommended amount of vitamin B12 in addition to folic acid. In a study looking at a different type of birth defect, a trans-NIH team found that about 20 percent of the incidence of isolated cleft lip may be due to a very tiny alteration in a gene involved in facial development. Oral-facial clefts are among the most common birth defects in the United States, arising from disruptions in a dynamic but still poorly understood interplay of genes, diet, and environment.

- Molloy AM, et al. *Pediatrics* 2009;123(3):917-23. PMID: 19255021.
  Rahimov F, et al. *Nat Genet* 2008 Nov;40(11):1341-7. PMID: 18836445.
  PMCID: PMC2691688.
- For more information, see http://www.genome.gov/27530477
- For more information, see http://www.genome.gov/27528380
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Genomics*
- (E, I) (**NHGRI**, NICHD, NIDCR)

The Collaborative Study on the Genetics of Alcoholism (COGA): In its 20th year, COGA is a multisite, multidisciplinary family study with the overall goal of identifying and characterizing genes that contribute to the risk for alcohol dependence and related phenotypes. COGA investigators have collected data from more than 300 extended families (consisting of more than 3,000 individuals) that are densely affected by alcoholism, enabling researchers to take a multigenerational perspective. A recent COGA study focusing on adolescents follows individuals longitudinally as they transition through the age of risk. Investigators have identified several genes, including *GABRA2, ADH4, ADH5, CHRM2, GRM8, GABRR1,* and *GABRR2* (*Rho 1* and *2*) that influence the risk for alcoholism and related behaviors, such as anxiety, depression, and other drug dependence. In addition to genetic data, extensive clinical neuropsychological, electrophysiological, and biochemical data have been collected, and a repository of immortalized cell lines from these individuals has been established to serve as a permanent source of DNA for genetic studies. These data and biomaterials are distributed to qualified investigators in the greater scientific community to accelerate the identification of genes that influence vulnerability to alcoholism. COGA will continue to identify genes and variations within the genes that are associated with an increased risk for alcohol dependence and will perform functional studies of the identified genes to examine the mechanisms by which the identified genetic variations influence risk.

- Xuei X, et al. *Am J Med Genet B Neuropsychiatr Genet* 2009;150B(3):359-68. PMID: 19536785. PMCID: 2829340.
- For more information, see http://zork.wustl.edu/niaaa
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*
- (E) (**NIAAA**) (GPRA)

EARLI, the Early Autism Risk Longitudinal Investigation: EARLI, the Early Autism Risk Longitudinal Investigation, comprises a network of leading autism researchers from three regions across the country. EARLI is following a cohort of 1,200 mothers of children diagnosed with autism who are pregnant or planning a pregnancy. The EARLI network will study how genetics and environmental factors work together to cause autism by studying families who already are affected by autism. Data will be collected prospectively via clinical assessment, interviews, self-reports, medical record review, home environment assessments, and biologic samples that will be used in current analysis and stored for future studies. Planned analyses include a determination of whether in utero exposure to organic pollutants such as polychlorinated biphenyls (PCBs), brominated diphenyl ethers (BDEs), and persistent organic pollutants (POPs) is associated with autism risk.

- For more information, see http://earlistudy.org
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (**NIEHS**)

Addressing the Heterogeneity of Autism Spectrum Disorders: NIH released a series of Funding Opportunity Announcements (FOAs), supported by funds from the American Recovery and Reinvestment Act of 2009, soliciting applications for 2-year research projects to address the heterogeneity of Autism Spectrum Disorders (ASD). This initiative represents the largest NIH funding opportunity for research on ASD to date and will jump-start many of the short-term objectives set forth in the Interagency Autism Coordinating Committee's Strategic Plan for Autism Spectrum Disorder Research. The FOAs target research in areas such as measurement development, biomarkers, immune and central nervous systems interactions, genetics, environmental risk factors, model development, treatment and intervention, and services research.

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-170.html
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-171.html
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-172.html
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-173.html
- For more information, see http://www.nimh.nih.gov/science-news/2009/rising-to-the-challenge-nih-will-use-60-million-in-recovery-act-funds-to-support-strategic-autism-research.shtml
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research*
- (E) (**NIMH**, NICHD, NIDCD, NIEHS, NINDS) (ARRA)

Insights into the Molecular Interplay Governing Formation of Cranial Sensory Ganglia: The developmental biology underlying sensory nerve development is fascinatingly intriguing. Take the trigeminal ganglion, which is responsible for touch, pain, and temperature sensation for most of the face. How do precursor cells self-organize in the embryo to produce an anatomically correct sensory network connecting to the central nervous system? Many of the answers are wired into the molecular circuitry of two transient embryonic cell types called neural crest cells and ectodermal placodes. They interact during embryonic development to differentiate into the nerve cells that form the trigeminal ganglion. But virtually nothing is known about the molecular interplay

that mediates this interaction. It is a biological puzzle with no known pieces. Now NIH grantees have introduced the first two pieces of the puzzle. They demonstrated in animal studies that the cranial subtype of neural crest cells express the protein Slit1 on their surface during their programmed migration to the trigeminal-forming ectodermal placodes. Meanwhile, as the trigeminal placode cells follow their developmental program, they express on their surface the Robo2 protein, which is the receptor for the Slit1 protein. The Robo2-Slit1 connection, like fitting a hand in a glove, mediates the interaction of neural crest and trigeminal placode cells during the formation of sensory ganglia. When the scientists disrupted one or both molecular signals, the resulting sensory ganglia were abnormal. The teams' findings are important to understanding the mechanisms that regulate formation of the sensory nervous system and thus provide potential targets for identifying the causes of congenital sensory disorders involving the neural crest cell population.

- Shiau CE, et al. *Nat Neurosci* 2008;11(3):269-76. PMID: 18278043.
- For more information, see http://www.nidcr.nih.gov/Research/ResearchResults/ScienceBriefs/Archive/archive2008/April/TrigeminalGanglion.htm
- For more information, see http://www.ncbi.nlm.nih.gov/pubmed/18278043?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (**NIDCR**)

Magnetic Resonance Imaging; Study of Normal Brain Development: Understanding healthy brain development is essential to finding the causes of many childhood disorders, including those related to intellectual and developmental disabilities, mental illness, drug abuse, and pediatric neurological diseases. NIH is creating the Nation's first database of MRI measurements and analytical tools, and clinical and behavioral data to understand normal brain development in approximately 500 children from across the Nation. This large-scale longitudinal study uses several state-of-the-art brain-imaging technologies. Anatomical neuroimaging scans; demographic, medical, cognitive, and behavioral data; and magnetic resonance spectroscopy data now are available to the research community via the NIH MRI Study of Normal Brain Development website.

- For more information, see http://www.bic.mni.mcgill.ca/nihpd/info/index.html
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E/I) (**NICHD**, NIDA, NIMH, NINDS) (GPRA)

Brain Matures a Few Years Late in ADHD: NIH-supported research on brain development in children with attention-deficit/hyperactivity disorder (ADHD) showed a normal pattern of brain development, but with a striking delay in cortical maturation. Between ages 5 and 15, the maturation of the prefrontal cortex was found to be delayed by roughly 3 years in children with ADHD compared to age-matched children without the disorder. Current studies now are exploring the effects of treatment on the rate of cortical maturation.

- Shaw P, et al. *Proc Nat Acad Sci U S A* 2007;104(49):19649-54. PMID: 18024590. PMCID: PMC2148343.
- For more information, see http://www.nimh.nih.gov/science-news/2007/brain-matures-a-few-years-late-in-adhd-but-follows-normal-pattern.shtml
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter

2: *Life Stages, Human Development, and Rehabilitation*
- (I) (**NIMH**)

The Role of Development in Drug Abuse Vulnerability: NIH supports animal, clinical, and epidemiological research across the lifespan to examine how developmental stage may influence drug abuse vulnerability or protection. The discovery of a protracted period of brain changes during early development and beyond has been critical to understanding the role of brain maturation in decision-making processes and responses to stimuli, including early (e.g., in utero) exposure to drugs. Adolescence has emerged as a particularly vulnerable period, during which an immature brain circuitry can translate into a preponderance of emotional reactivity (vs. higher cognitive control) that gives rise to the impulsive characteristics of many teenagers. This in turn may lead to dangerous risk-taking, such as experimenting with drugs that ultimately can lead to addiction. Using both animal models and clinical research, scientists are beginning to understand how environmental variables can play a key role in shaping brain maturation trajectories. In this regard, imaging, genetic, and epigenetic tools are helping interpret the effects of myriad environmental influences, such as quality of parenting, drug exposure, socioeconomic status, and neighborhood characteristics on brain development and behavior. In addition, the field of social neuroscience is harnessing the power of multidisciplinary approaches to tease apart these multilevel phenomena to better understand, for example, the neural mechanisms of peer pressure, the connections between chronic stress and risk of drug abuse initiation, and the impact that different early rearing environments can have on gene expression and behavior.

- For more information, see http://www.nida.nih.gov/tib/prenatal.html
- For more information, see http://www.nida.nih.gov/scienceofaddiction/
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (**NIDA**, NICHD) (GPRA)

Preventing Drug Abuse in Children and Adolescents: Intervening early to reduce risk factors for drug abuse and related problem behaviors can have tremendous impact and improve the trajectory of a young life. NIH is using a multipronged approach to achieve more effective substance abuse prevention by: (1) developing novel strategies, (2) exploring long-term and crossover effects of proven programs, and (3) improving adoption and implementation of evidence-based approaches. Innovative ideas being explored include physical activity to counter drug use, interactive Web-based technologies to engage young people, and brain imaging results to better target media messages. NIH also is building on proven methods such as universal prevention programs, which can reduce an array of risk behaviors, including substance abuse. These programs typically target behaviors appropriate to a child's developmental stage and have been shown to achieve long-term effects. For example, fifth graders who participated in the school-based prevention program "Positive Action" as first graders were about half as likely to engage in substance abuse, violent behavior, or sexual activity as those who did not. Similarly, exposure to the "Good Behavior Game," designed to reduce aggressive, disruptive behavior in first and second grade classrooms, led to fewer drug and alcohol disorders, lower rates of regular smoking, less antisocial personality disorder, and reduced delinquency and violent crime in young adults. However, the development of evidence-based prevention programs is meaningless unless they are adopted by communities. Therefore, NIH also is striving to increase implementation of successful prevention approaches in U.S. schools and

communities.

- Beets MW, et al. *Am J Public Health* 2009;99(8):1-8. PMID: 19542037.
  Kellam SG, et al. *Drug Alcohol Depend* 2008;95 Suppl 1:S5-S28. PMID: 18343607. PMCID: PMC2512256.
  Spoth R, et al. *Am J Prev Med* 2007;32 (5):395-402. PMID: 17478265.
- For more information, see http://www.nida.nih.gov/scienceofaddiction/
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research*
- (E) (**NIDA**)

Underage Drinking Research Initiative: In 2004, NIH launched its Underage Drinking Research Initiative with the goal of obtaining a more complete and integrated scientific understanding of the environmental, biobehavioral, and genetic factors that promote initiation, maintenance, and acceleration of alcohol use among youth, as well as factors that influence the progression to harmful use, abuse, and dependence—all framed within the context of overall human development. Activities and accomplishments in 2008 and 2009 include: (1) working with the Office of the Surgeon General to disseminate *The Surgeon General's Call to Action to Prevent and Reduce Underage Drinking*, including state roll-outs in Oklahoma, Ohio, Nebraska, Wyoming, Montana, Maryland, and Rhode Island (in addition to the six held in 2007); (2) continuing to convene scientific meetings of experts to advance underage drinking research. A series of meetings focusing on the development of guidelines and recommendations for screening children and adolescents for risk for drinking, alcohol abuse, and alcohol use disorders continued in 2008-2009; (3) issuing RFAs and program announcements (PAs), including "Limited Competition: Underage Drinking: Building Health Care System Responses (Phase II)" (RFA-AA-09-001) and "Alcohol, Decision-Making, and Adolescent Brain Development" (PA- 09-097 (R01) and PA-09-096 (R21)); (4) published "A Developmental Framework for Underage Alcohol Use"; and (5) published a *Pediatrics* supplement of seven developmentally focused papers covering a broad range of underage drinking topics.

- A Developmental Perspective on Underage Alcohol Use. *Alcohol, Research and Health* 2009;32(1). Available at: http://pubs.niaaa.nih.gov/publications/arh321/toc32-1.htm.
  Masten AS, et al. *Pediatrics* 2008;121 Suppl 4:S235-51. PMID: 18381492. Available at: http://pediatrics.aappublications.org/cgi/reprint/121/Supplement_4/S235.
- For more information, see http://www.niaaa.nih.gov/AboutNIAAA/NIAAASponsoredPrograms/underage.htm
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E, O) (**NIAAA**)

Neuroplasticity: Substrates for Change and Repair

Advances in Mental Health Treatment Development: NIH continues to fund research into the development of targeted medications and treatments for mental disorders.

- *Novel NeuroAIDS Therapies:* Integrated Preclinical/Clinical Program (IPCP): The IPCP supports drug development efforts focused on new targets that may modulate immune responses and protect brain cells in the context of HIV infection. One NIH-supported group will develop the use of nanotechnology to enhance delivery of HIV drugs to the brain. Another research group will

investigate the therapeutic potential of various compounds to treat or prevent HIV-associated mental disorders.

- *Innovative Approaches to Personalizing the Treatment of Depression:* NIH will advance research on individualizing the treatment of depression by supporting efforts to develop models and test new approaches that, by accounting for patient characteristics, aim to be more specific and thus potentially lead to more effective and efficient treatment interventions. Several studies will be supported through this initiative.
- *Fast-Acting Depression Treatments:* Previous NIH-funded research found that ketamine can lift depression in just hours, instead of the weeks it takes conventional antidepressants. NIH researchers now have identified a marker that predicts a patient's response using the split-second accuracy of magentoencephalography. Depressed patients showed increased activity in the anterior cingulate cortex (ACC; a region found in brain imaging studies to signal better treatment responsiveness) that correlated with their response to ketamine while viewing certain visual stimuli. This ACC activity may indicate the dysfunctional workings of the brain circuit that is targeted by ketamine.

    - Salvadore G, et al. *Biol Psychiatry* 2009;65(4):289-95. PMID: 18822408. PMCID: PMC2643469.
    - For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-040.html
    - For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-010.html
    - This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
    - (E/I) (**NIMH**)

Clinical Trials Networks for the Treatment of Mental Disorders: NIH is using its extensive clinical trials networks as platforms for investigating effective treatments for mental disorders. The networks, which are maintained through infrastructure supported by NIH, evolved from a recent series of practical clinical trials. The networks comprise more than 60 sites throughout the United States that maintain continual outreach efforts to diverse groups of patients and families with mental illnesses. The Bipolar Trials Network is conducting the Lithium Use for Bipolar Disorder (LiTMUS) trial, which will study the use of moderate-dose lithium for the treatment of bipolar disorder among 264 participants. The Depression Trials Network is seeking participants for the Combining Medications to Enhance Depression Outcomes (CO-MED) trial. This study will examine for the first time whether two different medications, when given in combination as the first treatment step, compared to one medication, will enhance remission rates, increase speed of remission, be tolerable to the participant, and provide better sustained benefits in the longer term. Results of this study, involving 660 participants, will inform practitioners in managing the treatment of patients with chronic or recurrent depression.

- For more information, see http://www.clinicaltrials.gov/show/NCT00667745
- For more information, see http://www.clinicaltrials.gov/show/NCT00590863
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
- (E) (**NIMH**)

New Genetics/Epigenetic Tools Shed Light on Addiction: NIH-supported research is taking full advantage of expanding databases and fast technologies to identify links between genetic variations and disease, health, and behavior. Such genetic studies are critical to teasing apart the

molecular mechanisms underlying complex diseases like addiction, which genes strongly influence. Investigators studying various neurological and psychiatric illnesses have already linked certain genes with specific diseases using custom screening tools known as "gene chips" (e.g., the neurexin gene has been found to play a role in drug addiction). Applying these tools to addiction and other brain disorders advances our understanding not only of vulnerability to addiction and its frequent comorbidities, but also of ways to target treatments based on a patient's genetic profile. To complement these efforts, NIH is investing in the equally important field of epigenetics, which focuses on the lasting modifications to the DNA structure and function that result from exposure to various stimuli. Attention to epigenetic phenomena is crucial to understanding the interactions between genes and the environment, including the deleterious long-term changes to brain circuits from drug abuse. For example, using a powerful new technique known as ChIP-on-chip to monitor epigenetic changes correlated with gene activity, investigators recently have mapped the genomic effects of chronic cocaine use in the reward center of the mouse brain. Such analyses provide needed information about which genes are altered by cocaine and can point to new targets for medications development. Epigenetic discoveries also can inform ways to smartly alter environmental factors so as to decrease the risk for drug abuse and addiction.

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-09-015.html
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-09-016.html
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-09-003.html
- For more information, see http://nihroadmap.nih.gov/epigenomics/initiatives.asp
- For more information, see http://nihroadmap.nih.gov/commonfundupdate.asp
- This example also appears in Chapter 3: *Genomics*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
- (E/I) (**NIDA**, NCI, NIAAA, NIMH) (GPRA)

Genes Involved in the Regulation of Sensitivity to Alcohol: Low doses of alcohol are stimulating in both humans and animals while higher doses have sedating effects. Sensitivity to alcohol, however, varies across individuals and low sensitivity to alcohol is a risk factor for the development of alcohol dependence in humans. Research with individuals who have a high family history of alcoholism seeks to understand how low response to alcohol contributes to dependence and how it can be used to predict risk for future alcohol problems. Research with animals is useful in identifying the mechanism(s) underlying the level of sensitivity to alcohol. Recently, a study with fruit flies implicated the Epidermal Growth Factor Receptor (EGFR) signaling pathway in regulating sensitivity to alcohol. Importantly, FDA-approved medications that inhibit EGFR increase alcohol sensitivity in mice and decrease alcohol intake in rats, suggesting that these drugs may offer therapeutic opportunities for treatment of alcohol use disorders in humans.

- Corl AB, et al. *Cell* 2009;137(5):949-60. PMID: 19464045.
  Trim RS, et al. *Alcohol Clin Exp Res* 2009;33(9):1562-70. PMID: 19485971.
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (**NIAAA**)

Chemical Messengers in the Brain Determine the Response to Stress and Regulate Craving For Alcohol: Stress contributes to many disease states, including alcohol dependence.

As alcohol dependence evolves, stress systems in the brain play an increasing role in continued alcohol use and relapse. Furthermore, individuals differ widely in response to stress. NIH researchers have investigated specific chemical messengers in the brain and the roles these messengers play as mediators of behavioral stress responses and their contributions to alcohol dependence. For example, the chemical messenger neuropeptide Y (NPY) is expressed in regions of the brain implicated in arousal and in determining emotional states. Production of NPY increases in these brain regions in response to emotionally charged and stressful conditions. Higher levels of NPY are associated with lower levels of alcohol consumption. NIH researchers also have made progress in studies of another brain messenger involved in stress responses, Neurokinin 1 (NK1) and its receptor (NK1R). In a clinical study, alcohol-dependent inpatients who recently stopped drinking were treated with a drug that blocks the actions of NK1R. Patients treated with the NK1R blocker exhibited reduced alcohol cravings, improved overall well-being, and reduced blood levels of stress hormones. Brain imaging during responses to stimulation that increases the likelihood of drinking showed a beneficial effect by the drug, suggesting that such drugs could reduce relapse in alcohol-dependent individuals.

- Zhou Z, et al. *Nature* 2008;452(7190):997-1001. PMID: 18385673. PMCID: PMC2715959. George DT, et al. *Science* 2008; 319(5869):1536-9. PMID: 18276852.
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E/I) (**NIAAA**)

Programs to Accelerate Medication Development for Alcoholism Treatment: Alcohol dependence is a complex heterogeneous disease caused by the interaction between multiple genetic and environmental factors that differ among individuals. Therefore, a diverse repertoire of medications is needed to provide effective therapy to a broad spectrum of alcohol-dependent individuals. Although promising compounds have been identified, developing medications is a long and costly process with a low probability of success for any single agent. NIH has initiated collaborations with the pharmaceutical industry to ensure its interest in taking promising compounds through the final phase of clinical trials and subsequent FDA consideration. As part of this approach, two new programs have been initiated:

- Laboratories have been established to screen promising compounds with animal models, enabling faster determination of those that merit advancement to large, multisite studies. Animal studies already have produced several targets for human studies that now are underway. The animal models are being validated using medications that have been tested clinically.
- A network of sites is being developed to conduct early Phase II proof-of-concept human trials. NIH will encourage the pharmaceutical industry to screen proprietary compounds in the preclinical models and, when results are positive, test them in the early Phase II human trials network. Currently quetiapine and levetiracetam are being evaluated in this network.
- Pharmacogenetic studies are ongoing to determine genetic variants that predict success for various medications.

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
- (E/I) (**NIAAA**) (GPRA)

A Multidisciplinary Approach to Tobacco Addiction: Tobacco addiction is the number one preventable public health threat, with enormous associated morbidity, mortality, and economic costs. Cigarette smoking—powerfully addictive mainly because of the key ingredient nicotine—is the

greatest preventable cause of cancer, accounting for at least 30 percent of all cancer deaths, 87 percent of lung cancer deaths, and nearly 80 percent of deaths from chronic obstructive pulmonary disease, according to CDC. CDC also reports that these leading causes of death could become relatively uncommon in future generations were the prevalence of smoking substantially reduced. In that vein, NIH-supported research has led to major advances in critical areas that together could greatly enhance our ability to either prevent or mitigate the impact of tobacco addiction. Convergent genomic studies recently have uncovered several genes previously not associated with nicotine reward or addiction that convey increased risk for addiction. This finding identifies markers of vulnerability, as well as new targets for medications development, with the potential to personalize, and thereby improve, treatment based on patients' genetic profiles. Clinical trials are exploring new medications and behavioral therapies for tobacco addiction. A promising approach, which already completed Phase II clinical testing, is that of immunotherapy. A nicotine vaccine (NicVAX), which binds nicotine in the blood, preventing it from ever reaching the brain, showed strong positive results in promoting abstinence among study participants who achieved sufficient antibody levels. Further studies are helping to define optimal protocols for vaccination to improve results in all smokers. This may be a particularly useful tool for tobacco cessation programs in the not-too-distant future.

- Centers for Disease Control and Prevention. Annual smoking-attributable mortality, years of potential life lost, and productivity losses United States, 1997-2001. *Morb Mortal Wkly Rep* 2005;54:625-8.
  Centers for Disease Control and Prevention. Smoking-attributable mortality, years of potential life lost, and productivity losses United States, 2000-2004. *Morb Mortal Wkly Rep* 2008;57(45):1226-28.
  Institute of Medicine. *Ending the Tobacco Problem: A Blueprint for the Nation.* Washington, DC: National Academies Press; 2007.
- For more information, see http://www.drugabuse.gov/ResearchReports/Nicotine/Nicotine.html
- For more information, see http://cdc.gov/tobacco/data_statistics/sgr/sgr_2004/index.htm
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (**NIDA**, NCI) (GPRA)

Transdisciplinary Tobacco Use Research Centers—Alcohol Use and Smoking: Multiple Institutes at NIH are co-funding seven collaborative, transdisciplinary centers to identify familial, early childhood, and lifetime psychosocial pathways related to smoking initiation, use, cessation, and patterns of dependence. Research on genetics of addiction, physiological biomarkers, and the use of advanced imaging techniques can lead to individualized and community approaches for tobacco prevention and treatment. This model demonstrates the feasibility and benefits of scientific collaboration across disciplines and public-private partnerships. Some recent highlights include: For smokers quitting while taking the prescription drug bupropion, the risk of smoking relapse was associated primarily with heavy, rather than with moderate drinking. Interactions between brain pathways activated by nicotine and alcohol may increase the likelihood of drinking in humans who simultaneously smoke and drink, suggesting that drugs that block nicotinic receptors also may help to reduce drinking. Varenicline, an agonist of certain nicotinic acetylcholine receptors, is a smoking cessation medication that has been shown in preclinical research to reduce alcohol drinking. Researchers are testing varenicline in preclinical models of ethanol drinking to determine which nicotinic receptor subtypes are most important. Recently, they found that varenicline reduces alcohol self-administration in heavy-drinking smokers.

- For more information, see http://dccps.nci.nih.gov/tcrb/tturc
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (**NIAAA**, NCI, NIDA)

The Critical Need for Addiction Medications: Breakthrough discoveries in the last decade have led to a profound transformation in understanding the mechanisms and consequences of drug abuse and addiction. The current picture offers a unique opportunity for the results of NIH's collective research to be translated into new, effective pharmacotherapies that could, either by themselves or with tested behavioral treatments, help alleviate the devastating personal and societal impacts of addiction. Distinct from the process that occurs with many other diseases, medications development for addiction suffers from minimal pharmaceutical industry involvement—likely because of real or perceived financial disincentives and stigma. Thus, despite many enticing scientific leads, we still have no medications available for stimulant, cannabis, inhalants, or polysubstance abuse, a gap that NIH is attempting to fill. Current efforts are capitalizing on a greater understanding of the neurobiology underlying addiction and of newly identified candidate systems and molecules. Several innovative treatment approaches—beyond targeting the brain's reward system—have proven feasible and are progressing to more advanced stages of research and development. Projects in this context include work on medications to diminish conditioned responses, promote new learning, and inhibit stress-induced relapse. In addition, vaccines (e.g., for nicotine, cocaine) are being developed that induce the body to produce drug-specific antibodies able to sequester drug molecules while they are still in the bloodstream and prevent them from entering the brain. Next-generation pharmaceuticals also will emerge from human genome studies uncovering novel targets for better tailoring of treatments according to a person's genes.

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
- (E) (**NIDA**) (GPRA)

Neurobiology of Appetite Control: NIH supports research to elucidate the complex biologic pathways that converge in the brain to regulate appetite. For example, the sight of food has been found to induce different responses in the brains of patients following weight loss; these differences are due to changes in levels of the hormone leptin. Researchers also discovered that rats susceptible to becoming obese from a high-calorie diet have fewer neural connections in the brain in the hypothalamus (the part of the brain that has a key role in weight regulation) compared to normal rats. Additionally, a factor secreted by the small intestine in response to dietary fat intake has been found to enter the brain and suppress appetite in rats. More recently, six new genetic regions associated with obesity were identified and found to be in or near genes expressed in the brain. To highlight further the connection between brain function and obesity, a trans-NIH workshop on neuroimaging in obesity research was held to share data and experiences with functional neuroimaging approaches to study brain involvement in various aspects of obesity such as weight gain and loss, and the neurotransmitters and brain structures associated with energy balance, hunger, and decision-making. A recent funding opportunity announcement was issued to foster new research using neuroimaging approaches to enhance understanding of food intake and energy expenditure in the context of obesity. This research has implications for new therapies for obesity.

- Rosenbaum M, et al. *J Clin Invest* 2008;118(7):2583-91. PMID: 18568078. PMCID: PMC2430499.

Bouret SG, et al. *Cell Metab* 2008;7:7(2):179-85.PMID: 18249177. PMCID: PMC2442478.
Gillum MP, et al. *Cell* 2008;135(5):813-24.PMID: 19041747. PMCID: PMC2643061.
Willer CJ, et al. *Nat Genet* 2009;41(1):25-34. PMID: 19079261. PMCID: PMC2695662.

- For more information, see http://www3.niddk.nih.gov/fund/other/neuroimaging2008/
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/rfa-dk-08-009.html
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (**NIDDK**)

Understanding the Roles of Non-Neuronal Cells in Neuropathic Pain Provides New Targets for Intervention: Chronic pain caused by nerve injury, called neuropathic pain, is difficult to treat because we do not yet fully understand the biological mechanisms underlying its development and persistence. Most pain-relieving medications for chronic pain target nerve cells, yet it is becoming clear that non-nerve (non-conducting) cells also play an important role in some chronic pain conditions. Matrix metalloproteases (MMPs) are enzymes that break down the medium surrounding tissue cells. MMPs also activate several pro-inflammatory proteins that stimulate the non-nerve conducting function of of the supportive glial cell. Scientists are wondering if neuropathic pain and inflammation are linked by a common mechanism involving MMP activation. Researchers found that a specific matrix metalloprotease, MMP9, showed increased activity soon after nerve injury, which stimulated the glial cells in the spinal cord, but this increased activity declined after several days. A different enzyme, MMP2, also was increased, but at later times after injury; this increase led to activation of another nerve-supportive cell in the spinal cord. The research showed that the pain response of nerve-injured animals were blocked early by inhibitors of MMP9 or later by inhibitors of MMP2. These findings suggest an important role for MMP9 in the onset of chronic neuropathic pain conditions, and for MMP2 in the persistence of those conditions. The results also demonstrate the complex interplay between nerve cells and several non-nerve cells. This research describes a novel set of molecules involved in neuropathic pain, and points scientists toward new targets for possible interventions to short-circuit the onset and persistence of chronic pain conditions.

- Kawasaki Y, et al. *Nat Med* 2008;14(3):331-6. PMID: 18264108. PMCID: PMC2279180.
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (**NIDCR**)

Promising Approaches to Treating Chronic Pain: Opioid analgesics are the most powerful pain medications currently available; unfortunately, they can result in addiction, tolerance, and physical dependence, all of which may undercut their value in some patients. Thus, an area of enormous need is the development of potent analgesics with diminished abuse liability for treating chronic pain. In response, NIH has implemented an aggressive and multidisciplinary research program that is yielding tangible results, which stand to revolutionize the field of pain management. At the molecular level, cannabinoid (CB) research has shown that it is possible to activate the CB system selectively to provide analgesia with minimal or no effects on mental function, and no abuse liability. New findings in basic pharmacology reveal previously unrecognized complexity emerging from the natural mixing of different (heteromeric) receptors. Targeting them could provide a vastly expanded range of pharmacotherapeutics. This approach has already ushered in the development of promising designer molecules that can block pain more selectively and safely. At the cellular level, active research on non-neuronal brain cells has led to the realization that glia activation can amplify pain. This discovery suggests that targeting glia and their proinflammatory products may provide a

novel and effective therapy for controlling clinical pain syndromes and increasing the utility of other analgesic drugs. At the brain circuit level, a new approach has been developed to harness the brain's intrinsic capacity to train itself through a strategy in which subjects "learn" how to regulate pain by viewing, and then controlling, images of their own brains in real time.

- Varga EV, et al. *Curr Mol Pharmacol* 2008;1(3):273-84. PMID: 20021440.
  Ferre S, et al. *Trends Neurosci* 2007;30(9):440-6. PMID: 17692396.
  Daniels DJ, et al. *Proc Natl Acad Sci U S A* 2005;102(52):19208-13. PMID: 16365317. PMCID: PMC1323165.
  Ledeboer A, et al. *Expert Opin Investig Drugs* 2007;16(7):935-50. PMID: 17594181.
  deCharms RC. *Trends Cogn Sci* 2007;11(11):473-81. PMID: 17988931.
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (**NIDA**, NINDS)

Bioactive Nanostructures for Neural Regeneration: Spinal cord injury (SCI) often leads to permanent paralysis and loss of sensation below the site of injury because of the inability of damaged axons to regrow across the injury site in adults. Nanomaterials built from a family of self-assembling molecules may offer hope for treating serious injuries, such as spinal cord injury according to new results from NIH research. Recently, an NIH-supported research group developed peptide amphiphile (PA) molecules that self-assemble in vivo into supramolecular nanofibers and tested them on mouse models of spinal cord injury. In this work, in vivo treatment with the PA nanofibers, after SCI, reduced cell death and promoted regeneration of both motor fibers and sensory fibers through the lesion site. Treatment with the PA also resulted in significant behavioral improvement. These observations demonstrate that it is possible to inhibit glial scar formation and to facilitate regeneration after SCI using bioactive three-dimensional nanostructures displaying high densities of neuroactive epitopes on their surfaces.

- Tysseling-Mattiace VM, et al. *J Neurosci* 2008;28(14):3814-23. PMID: 18385339. PMCID: PMC2752951.
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Technology Development*
- (E) (**NIBIB**)

Neural Interfaces Program: Neural interfaces are systems that operate at the intersection of the nervous system and an internal or external device, including neural prosthetics. Neural prosthetic devices restore or supplement nervous system functions that have been lost through disease or injury, allowing people with disabilities to lead fuller and more productive lives. NIH pioneered the development of this technology, beginning more than 35 years ago. The program has, directly or indirectly, catalyzed the development of cochlear implants, which help people with hearing impairments; respiratory and hand grasp devices for people with spinal cord injuries; and deep brain stimulation for Parkinson's disease, among other contributions. Current work aims to restore voluntary bowel and bladder control and standing to spinal cord-injured persons, allow paralyzed persons to control devices directly from their brains, improve cochlear implants, and improve deep brain stimulation, which may be applicable to many brain disorders. Through the years, the program has fostered the development of a robust research community, now including private sector companies, and represents a cooperative effort among several ICs, which also coordinate their efforts with programs that now are underway in the Department of Veterans Affairs and Department of Defense.

- For more information, see http://www.ninds.nih.gov/funding/research/npp/index.htm
- For more information, see http://www.nih.gov/about/researchresultsforthepublic/CochlearImplants.pdf
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Technology Development*
- (E) (**NINDS**, NEI, NIBIB, NICHD, NIDCD)

Stem Cell Studies Provide Foundation for Possible Future Hearing Loss Treatments: Tiny cells inside your ear, known as hair cells, detect the vibrations in the air that constitute sound and turn them into electrical impulses that are sent to the brain. In mammals, when hair cells are damaged, the ability to detect sound is lost or compromised because hair cells cannot be replaced. Once the hair cells are lost, the sensory cells that are next in the relay of sound information, known as spiral ganglion neurons (SGNs), also are at risk of dying due to lack of input. Scientists are working to replace lost or damaged hair cells and their SGNs in the hope of restoring lost hearing. NIH-supported scientists discovered that a specific population of cells from the inner lining of the adult mouse brain (ependymal cells), which arise during development from the same part of the brain that produces hair cells, are capable of dividing and share important similarities with hair cells. This population of cells also is found in the adult human brain. In related studies, the scientists also isolated mouse neural stem cells (NSCs) that are capable of differentiating into neurons that exhibit SGN-like properties. When cocultured with mouse SGNs, both NSCs and ependymal cells formed active connections with the SGNs. This research suggests that stem cells isolated from an adult brain may be able to replace lost inner-ear sensory cells and the neurons that connect these cells to the brain. These findings may provide a foundation for future treatments for hearing loss.

- Wei D, et al. *Proc Natl Acad Sci U S A* 2008;8-9. PMID: 19064919. PMCID: PMC2634930.
- (E) (**NIDCD**)

Neurodegeneration: Fighting the Effects of Age, Exposure, and Disease

Translational Research on Alzheimer's Disease (AD): To move basic research on AD and associated disorders into translational research and drug testing in clinical trials, this initiative includes drug discovery, preclinical development, and a program of toxicology services for academic and small business investigators who lack the resources to perform the required toxicology studies on promising therapeutic compounds. A number of agents are undergoing testing, including antihypertensives, anti-inflammatory drugs, and novel small molecules. In addition, in recent years, NIH-supported basic research has contributed to industry development of new Alzheimer's disease drugs. This program is a cornerstone of the NIH GPRA goal to "by 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease."

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-07-048.html
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research*
- (E) (**NIA**) (GPRA)

Grape Seed Extract May Help Neurodegenerative Diseases: Tauopathies—a group of neurodegenerative conditions such as Alzheimer's disease—have been linked to the build-up of

"misfolded" tau proteins in the brain. (Tau proteins are associated with microtubules, which help to regulate important cellular processes.) In light of previous studies indicating that grape-derived polyphenols may inhibit protein misfolding, an NIH-funded research center examined the potential role of a particular grape seed polyphenol extract (GSPE) in preventing and treating tau-associated neurodegenerative disorders. In one study, the researchers found that this GSPE reduced Alzheimer's-type neuropathology and cognitive decline in a mouse model of Alzheimer's disease and inhibited an Alzheimer's-linked process called cerebral amyloid deposition. In another study, the researchers used a variety of analytical techniques to clarify further how the GSPE produces its effects. The results of their preclinical study showed that GSPE interferes with the generation of tau protein aggregates and also disassociates preformed aggregates. Thus, GSPE may affect processes critical to the onset and progression of neurodegeneration and cognitive dysfunctions in tauopathies. The studies' findings, together with indications that this GSPE is likely to be safe and well-tolerated in people, support further exploration and development of GSPE as a therapy for Alzheimer's disease.

- Ho L, et al. *J Alzheimers Dis* 2009;16(2):433-9. PMID: 19221432. PMCID: PMC2800939. Ono K, et al. *J Biol Chem* 2008;283(47):32176-87. PMID: 18815129. PMCID: PMC2583320. Wang J, et al. *J Neurosci* 2008 Jun 18;28(25):6388-92. PMID: 18562609. PMCID: PMC2806059.
- For more information, see http://nccam.nih.gov/research/results/spotlight/031209.htm
- This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- (E) (**NCCAM**)

Alzheimer's Disease Cooperative Study (ADCS): Much of the AD-related clinical research supported by NIH takes place through the ADCS. The study involves a consortium of centers in the U.S. and Canada where clinical trials are carried out on promising new therapies that may preempt the onset of AD or predict development of the disease in vulnerable people. To date, approximately 4,600 people have participated in the trials. Five new trials are underway through ADCS. These include: (1) a trial to examine whether treatment with DHA, an omega-3 fatty acid, will slow decline in AD; (2) a multicenter trial to evaluate home-based assessment methods for AD prevention research in people age 75 or older; (3) a trial to evaluate the efficacy and safety of 18 months of treatment with the drug PF-04494700 (TTP488), an oral compound formulated to prevent amyloid beta from binding to a specific brain receptor; (4) a trial of valproate, an anticonvulsant drug, to determine its ability to delay the emergence of agitation and psychosis and possibly the clinical progression of AD; and (5) a trial of intravenous immunoglobulin, which contains naturally occurring antibodies against beta-amyloid, to establish its clinical utility for treating AD. This program is a cornerstone of the NIH GPRA goal to: "By 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease."

- For more information, see http://www.adcs.org/Default.aspx
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research*
- (E) (**NIA**) (GPRA)

Ginkgo Evaluation of Memory (GEM) Study Shows No Benefit in Preventing Dementia in the Elderly: Dementia is a loss of brain function that causes serious changes in memory, personality, and behavior. Alzheimer's disease, the most common form of dementia in older people, affects as many as 4.5 million Americans. Some people use extracts of leaves from the *Ginkgo biloba* tree in an effort to prevent or treat Alzheimer's and other types of dementia. NIH-supported

researchers tested ginkgo in a large sample of older adults to see whether it could prevent or delay the onset of dementia, particularly Alzheimer's. The study enrolled 3,069 participants ages 75 or older who had normal cognition or mild cognitive impairment. For about 6 years, they took twice-daily doses (120 milligrams) of either ginkgo extract or a placebo. The study found that ginkgo did not lower the overall incidence of dementia or Alzheimer's. Nevertheless, the study demonstrates the feasibility of large dementia prevention trials in older adults, and provides useful information about how to design and conduct such trials. The results of this study confirm the importance of randomized trials in determining therapeutic benefit of new approaches to dementia and Alzheimer's disease. The results also provide a wealth of information that will be valuable in designing future clinical trials. Future analyses of the data will provide additional information on ginkgo's possible effects on cardiovascular disease, cancer, depression, and other age-related conditions. They also may identify subgroups at greater risk for developing dementia.

- Kinlock TW, et al. *J Subst Abuse Treat* 2009;37(3):277-85. PMID: 19017911. PMCID: PMC2823569.
- For more information, see http://nccam.nih.gov/research/results/gems/
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (**NCCAM**, NHLBI, NIA, NINDS, ODP/ODS)

Progress in Parkinson's Disease Research: For the past 7 years, NIH actively has been engaged in identifying gaps in Parkinson's disease research and developing programs to address them. Examples of progress include initiation of Phase III clinical trials of creatine and coenzyme Q10 to treat early Parkinson's disease; development of diagnostic criteria for depression and psychosis in people with Parkinson's disease; and support for a Parkinson's disease Gene Therapy Study Group. In 2009, a major clinical trial cofunded by NIH and the Veterans Administration published its finding that Deep Brain Stimulation is more effective than standard drug therapy for Parkinson's disease but also carries a higher risk of adverse events. NIH also has begun to formally assess the effectiveness of its programs by completing an evaluation of its Morris K. Udall Centers of Excellence in Parkinson's Disease Research. This evaluation included an assessment of scientific progress made by the centers and the value of using a centers mechanism, as well as an exploration of the effectiveness of program management and review in supporting the centers. The Working Group tasked with this evaluation released its findings in September 2007.

- Weaver FM, et al. *JAMA* 2009;301(1):63-73. PMID: 19126811.
- For more information, see http://www.ninds.nih.gov/funding/research/parkinsonsweb/index.htm
- For more information, see http://www.parkinsontrial.ninds.nih.gov/index.htm
- For more information, see http://www.ninds.nih.gov/news_and_events/press_releases/pressrelease_creatine_03222007.htm
- For more information, see http://www.ninds.nih.gov/udall_centers_evaluation
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (**NINDS**)

Centers for Neurodegenerative Science: NIH has awarded three Centers for Neurodegeneration Science program grants to conduct research that combines human studies with basic mechanistic research to understand how environmental factors contribute to the origins, progression, treatment, and prevention of neurodegenerative diseases. The three projects will focus on investigating Parkinson's disease (PD). PD is linked to pesticide exposure, mitochondrial damage,

and altered storage of dopamine. One project will look at how environmental and genetic factors interact in PD pathogenesis and search for biomarkers that will help identify people at risk for developing PD. A second project will investigate the importance of the ubiquitin-proteasome system, microtubules, and aldehyde dehydrogenase disruption by pesticides in conferring vulnerability to dopamine neurons. An integrated, multidisciplinary approach will be used to identify agricultural pesticides that are able to disrupt the same cellular pathways shown to alter the viability of dopaminergic neurons and determine whether these pesticides increase the risk of PD. The third project will focus on proteins known to be related to PD with the goal of determining how chemical reactions lead to damaging modifications of these proteins. Clinical implications will be explored through biomarker development and a screen to identify compounds that can preserve protein function by reducing free radical stress. The knowledge generated by these projects will provide therapeutic targets for disease intervention and prevention strategies.

- Yu T, et al. *Bioinformatics* 2009;25(15):1930-6. PMID: 19414529. PMCID: PMC2712336.
  Orr AG, et al. *Nat Neurosci* 2009;12(7):872-8. PMID: 19525944. PMCID: PMC2712729.
  Taylor TN, et al. *J Neurosci* 2009;29(25):8103-13. PMID: 19553450. PMCID: PMC2813143.
  Guillot TS, Miller TW. *Mol Neurobiol* 2009;39(2):149-70. PMID: 19259829.
  Cho DS, et al. *Science* 2009;324(5923):102-5. PMID: 19342591. PMCID: PMC2823371.
  Xiong H, et al. *J Clin Invest* 2009;119(3):650-60. doi: 10.1172/JCI37617. PMID: 19229105. PMCID: PMC2648688.
  Choo YS, Zhang Z. *J Vis Exp* 2009 Aug 19;(30). pii: 1293. doi: 10.3791/1293. PMID: 19692941.
- This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- (E) (**NIEHS**)

New Indications for Established Agents to Treat Chronic Disease: When identifying interventions to treat an illness or chronic condition, testing drugs that already have been developed for other conditions sometimes can be faster and more cost-effective than designing entirely new agents because drug safety profiles already have been established, and contraindications already are known. NIH intramural investigators currently are exploring the use of several established agents in the treatment of chronic disease. For example, a growing body of animal research suggests that the compound fenoterol, widely used for treatment of pulmonary disease, may be effective in the treatment of congestive heart failure. Experimental results with fenoterol are sufficiently encouraging to recommend advancing translational efforts and planning clinical trials. Other studies in animal models have shown that the drug erythropoietin, used to treat certain types of anemia, has a protective effect on the heart if administered shortly after a heart attack. Based on the results of these studies, researchers have initiated a study to assess the effects of erythropoietin (EPO) on the heart after a heart attack. Researchers also have reported preclinical data that suggest a therapeutic benefit of the diabetes drug exendin-4 in the treatment of stroke and Parkinson's disease.

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
- (I) (**NIA**)

Interventions to Remediate Age-Related Cognitive Decline: Age-related cognitive decline distinct from dementia will affect most older individuals to some extent and has a direct impact on their independence and vitality. Cognitive training, physical exercise, enhancement of self-efficacy, social engagement, diet, environmental enrichment, and stress reduction have all been shown to have positive effects on cognition; however, the quality of this evidence varies widely across studies.

NIH, in partnership with the McKnight Brain Research Foundation in conjunction with the Foundation for NIH, has initiated a program to convert insights from previous work in cognitive aging into feasible intervention strategies that can be tested in randomized clinical trials. The program's primary goal is to support the initial development and pilot testing of behavioral interventions (individually and in combination) to establish their feasibility, the likely strength of their effects, and immediate and short-term efficacy. These early steps should allow these interventions to move to new clinical trials.

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-09-009.html
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research*
- (E) (**NIA**)

Viewing Tinnitus in Action: Tinnitus is the perception of sound in the absence of sound (i.e., ringing, roaring, hissing, or clicking sounds in the ears). It is generally associated with age-related or noise-induced hearing loss. In the United States, it affects 12.3 percent of men and nearly 14 percent of women aged 65 and over, and it is the number one cause of service-connected disability for American veterans returning from Iraq and Afghanistan. Very little is known about the neural basis of the disorder. NIH-supported scientists studied a rat model of drug-induced tinnitus combined with brain imaging (microPET and MRI) techniques to identify brain regions in the rat that are affected during tinnitus. Two regions of the brain, consistent with those identified in humans experiencing either noise- or age-induced tinnitus, demonstrated increased activity during drug-induced tinnitus. This study is the first to demonstrate how microPET and MRI techniques can identify brain regions involved in tinnitus. This technique now may be used to study other causes of tinnitus (such as noise) and to evaluate the efficacy of potential therapeutic treatments for tinnitus.

- Paul AK, et al. *Neuroimage* 2009;44(2):312-8. PMID: 18948211. PMCID: PMC2613016.
- For more information, see http://www.nidcd.nih.gov/health/hearing/noiseinear.asp
- (E) (**NIDCD**)

Hearing Loss Is Common in People with Diabetes: In 2008, scientists supported by NIH analyzed data from the 1994-2004 National Health and Nutrition Examination Survey (NHANES), and discovered that hearing loss is about twice as common in adults with diabetes compared to those who do not have the disease. Earlier U.S. studies that examined diabetes and hearing loss found a weaker association or no association, but these studies were based on smaller samples of older adults, and they were not nationally representative (like NHANES). This is the first study of a nationally representative sample of working-age adults, ages 20 to 69 years old, and the data show an association between diabetes and hearing impairment evident as early as ages 30 to 40. Blood flow to the inner ear is essential for normal hearing. Diabetes may lead to hearing loss by damaging the nerves and blood vessels of the inner ear. Autopsy studies of individuals with diabetes have shown evidence of such damage. Additional studies into cochlear blood flow also may shed light on how hearing loss may occur more often in individuals with diabetes.

- Bainbridge KE, et al. *Ann Intern Med*. 2008;149(1):1-10.
- For more information, see http://www.nidcd.nih.gov/news/releases/08/06_18_08.htm
- (E/I) (**NIDCD, NIDDK**)

Neuroprotection Treatment Strategy in Glaucoma: Glaucoma is a group of eye disorders

that share a distinct type of optic nerve damage, in which retinal ganglion cells (RGCs) die. Glaucoma is a major public health problem and the leading cause of blindness in African Americans. Elevated intraocular pressure is a common, but not universal, feature of the disease, and pressure-reducing drugs and surgery have been found to delay and reduce severe vision loss from the disease. However, because optic nerve damage is common to all forms of glaucoma, regardless of intraocular pressure, more recent translational research efforts have been targeted toward neuroprotection of the optic nerve. Using gene transfer in a mouse model of glaucoma, NIH investigators overexpressed genes that encode two naturally occurring neuroprotective agents, ciliary-derived neurotrophic factor (CNTF) and brain-derived neurotrophic (BDNF) alone and in combination. Gene transfer with CNTF alone offered the best outcome with a 15 percent improvement in RGC survival compared to control animals. BDNF alone and in combination with CNTF offered modest but not statistically significant protection. Previous studies of CNTF in retinal degenerative diseases found that low doses were neuroprotective while higher doses led to toxicity. Future work will require that dose-response is carefully measured to deliver a safe, optimal therapeutic dose.

- Pease ME, et al. *Invest Ophthalmol Vis Sci* 2009;50(5):2194-200. PMID: 19060281.
- For more information, see http://www.iovs.org/cgi/content/full/50/5/2194
- (E) (**NEI**)

Toward Better Treatment for Muscular Dystrophy: NIH is pursuing multiple pathways to therapeutic development for the muscular dystrophies. NIH funded two new Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers in FY 2008: the Boston Biomedical Research Institute, which seeks to identify biomarkers that can be used in preclinical studies and clinical trials of potential facioscapulohumeral muscular dystrophy (FSHD) therapies, and a center at the University of North Carolina at Chapel Hill, which is developing and testing gene therapies for Duchenne muscular dystrophy (DMD) and other muscle disorders. Collectively, the Wellstone centers program is designed to accelerate the translation of fundamental scientific advances to the clinic (see Chapter 4) and to serve as a national resource for the muscular dystrophy community through core facilities and training programs. NIH funds multiple approaches to therapeutic development through projects outside of the Wellstone program, including a robust portfolio on translational research in muscular dystrophy. Research currently is solicited in this area through two Funding Opportunity Announcements (FOAs) released in 2008: Exploratory/Developmental Projects for Translational Research in Neuromuscular Disease (R21) and the Cooperative Program in Translational Research in Neuromuscular Disease (U01). Previous FOAs on Translational Research in Muscular Dystrophy resulted in a number of funded projects in this area, including projects to develop small molecule drugs and to develop effective gene therapy design and delivery approaches. Progress also is being made toward the GPRA goal to "advance two emerging strategies for treating muscular dystrophy to clinical trial readiness by 2013."

- For more information, see http://www.wellstonemdcenters.nih.gov/
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-229.html
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-228.html
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (**NINDS**, NHLBI, NIAMS, NICHD) (COE, GPRA)

Multiple Sclerosis Research: Although the exact cause of multiple sclerosis (MS) is unknown, recent research supported by NIH has begun to identify genetic variations associated with increased

risk for developing the disease. In 2007, a genome-wide association study with NIH support reported the first new genetic risk factors for MS to be identified in more than 20 years, and in 2009, meta-analyses and replication studies revealed additional new susceptibility genes. NIH also funds and conducts basic, translational, and clinical research on disease mechanisms, biomarkers, and treatments for MS. For example, NIH supports a randomized, double-blind, placebo-controlled Phase III trial (CombiRx) comparing the efficacy of treatment combining beta-interferon and glatiramer acetate vs. treatment with either agent alone for relapsing-remitting MS. The trial will determine whether combination therapy offers an improvement over the partial efficacy of either single treatment; it is the only direct comparison of these commonly used medications that is fully blinded and not supported by a commercial entity. NIH's Intramural Neuroimmunology Branch is collaborating with this trial to identify biomarkers associated with different clinical and treatment response profiles (BioMS). Such biomarkers may inform predictions about which treatment will most likely benefit a given patient, making this ancillary study an exciting addition to comparative effectiveness research in MS. Intramural investigators also will collaborate with the Swiss pharmaceutical company Santhera in a Phase I/II clinical trial to test the safety and efficacy of idebenone, which may protect against tissue damage, as a potential treatment for primary progressive MS.

- De Jager PL, et al. *Nat Genet* 2009;41(7):776-82. PMID: 19525953. PMCID: PMC2757648.
- For more information, see http://clinicaltrials.gov/ct2/show/NCT00211887
- For more information, see http://clinicaltrials.gov/ct2/show/NCT00325988
- For more information, see http://clinicaltrials.gov/ct2/show/study/NCT00950248
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Clinical and Translational Research*
- (E, I) (**NINDS**)

Advancing Neuroscience Research Through Collaboration

NIH Blueprint for Neuroscience Research: Since its inception in 2004, the NIH Blueprint has been a successful model of trans-NIH collaboration, bringing together 16 NIH ICs and Offices that support neuroscience research. The Blueprint catalyzes research progress by developing tools, resources, and training opportunities that transcend the mission of any single NIH IC and serve the entire neuroscience community. In FY 2008, the Blueprint launched initiatives to develop novel approaches for the study and manipulation of neural circuits as they form during development, a resource for creation and distribution of high-quality monoclonal antibodies for neurodevelopment research, and a gene expression map of the developing rhesus macaque brain. In FY 2009, the Blueprint released a funding announcement supporting research to develop probes, instrumentation, and other tools for understanding, monitoring, and manipulating neural plasticity. In addition, the Blueprint held a workshop focused on translating research on circuit-level plasticity to clinical applications. The Blueprint continues to support training in neuroscience research, clinical assessment tools for neurological and behavioral function, and widely used neuroimaging, neuroinformatics, and genetics and animal model resources. Looking forward, the NIH Blueprint plans to support initiatives addressing Grand Challenges in neuroscience in the areas of pain research, mapping of the human brain, and therapy development for diseases of the nervous system.

- For more information, see http://www.neuroscienceblueprint.nih.gov
- (E) (**NIH Blueprint**, NCCAM, NCRR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR,

NIEHS, NIGMS, NIMH, NINDS, NINR, OBSSR)

Blueprint Interdisciplinary Research Training: Under the auspices of the NIH Blueprint, interdisciplinary training programs have been established in computational neuroscience, neuroimaging, and translational research in the neurobiology of disease.

- The computational neuroscience programs seek to attract undergraduate and predoctoral students from the physical, mathematical, and engineering sciences to neuroscience research, and to expand the training of neuroscience students in quantitative sciences. Students learn how to develop models of neural systems or processes, test them experimentally, and then use experimental data to refine the models.
- The neuroimaging programs support predoctoral students and summer research intensives and provide comprehensive training in the breadth of imaging techniques and their application to neuroscientific questions. The goal of these programs is to train the next generation of neuroimaging researchers in the limitations, advantages, and underlying principles of currently available neuroimaging modalities.
- The translational research programs support students at multiple stages of their careers. The programs are designed to cross-train students in basic and clinical neuroscience, focusing not on specific diseases but on the biological mechanisms that are shared across diseases.

These Blueprint training programs are successfully seeding the field of neuroscience with highly qualified graduate students, postdoctoral fellows, and faculty.

- For more information, see http://neuroscienceblueprint.nih.gov/neuroscience_resources/training.htm
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Research Training and Career Development*
- (E) (**NIH Blueprint**, NCCAM, NCRR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR, OBSSR)

National Database for Autism Research: The National Database for Autism Research (NDAR) is a collaborative biomedical informatics system created by NIH to provide a national resource to support and accelerate research in autism spectrum disorder (ASD). NDAR hosts human genetic, imaging, and phenotypic research data relevant to ASD, making these data available to qualified researchers. NDAR also has the capability to allow investigators to use NDAR for data sharing among select collaborators in ongoing studies. Through its Data Dictionary, NDAR will foster the development of a shared, common understanding of the complex data landscape that characterizes ASD research. Finally, its architecture facilitates linkage of NDAR with other significant data resources, regardless of their location or ownership and in ways that respect the policies and implementations of those other data resources.

- For more information, see http://ndar.nih.gov/
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (E/I) (**NIMH**, CIT, NICHD, NIDCD, NIEHS, NINDS)

A Clearinghouse for Neuroimaging Informatics Tools and Resources: Many neuroimaging tools and databases are underutilized because they cannot be found easily, are not user-friendly, or are not easily adoptable or adaptable. In an effort to promote the enhancement,

adoption, distribution, and evolution of neuroimaging informatics tools and resources, the NIH Blueprint for Neuroscience Research has launched the Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC). Examples of included tools are: image segmentation, image registration, image processing pipelines, statistical analysis packages, spatial alignment and normalization algorithms, and data format translators. Resources include: well-characterized test datasets, data formats, and ontologies. Since the first release in October 2007, the clearinghouse website, or NITRC, has become host to 180 tools and resources, with a community of 13,602 unique visitors who downloaded NITRC tools and resources, and 7,000 unique visitors per month, more than 954 of which are registered users (11 percent non-English speaking). The hits to the site have reached 15,635,019/month. Since its inception, more than 50,000 software files have been downloaded. More than 53 percent of the tools on NITRC had not been shared online previously but now are available to the community. In 2009, the NITRC project won the first place of Excellence.gov awards, the largest Federal government award program to recognize the very best in government IT programs, among 61 competitors. Through the initiative, nearly 40 awards have been made to neuroimaging tools and resource developers to enhance the accessibility, interoperability, and adoptability of their existing tools and resources.

- Ardekani BA, Bachman AH. *Neuroimage* 2009;46(3):677-82. PMID: 19264138. PMCID: PMC2674131.
- For more information, see http://www.nitrc.org/
- For more information, see http://neuroscienceblueprint.nih.gov/
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems* and Chapter 3: *Technology Development*
- (E) (**NIH Blueprint**, NCCAM, NCRR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR, OBSSR)

NINDS Human Genetics Repository: In 2002, NINDS established the Human Genetics Repository to collect, store, characterize, and distribute DNA samples and cell lines and standardized clinical data for the research community. By June 2009, the repository held material from 27,166 subjects, including those with cerebrovascular disease (8,625), epilepsy (1,356), Parkinson's disease (5,700), motor neuron diseases such as amyotrophic lateral sclerosis, also known as Lou Gehrig's disease, (2,631), and Tourette Syndrome (1,185), as well as control samples (6,162). The ethnically diverse collection represents populations from the United States and several other countries. Investigators have submitted or published more than 100 scientific articles based on data from this resource, and technological advances allowing whole genome screening for disease genes also have enhanced its value.

- For more information, see http://ccr.coriell.org/Sections/Collections/NINDS/?SsId=10
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (E, I) (**NINDS**)

Alzheimer's Disease Neuroimaging Initiative (ADNI): ADNI is an innovative public-private partnership for examining the potential for serial magnetic resonance imaging, positron emission tomography, or other biomarkers to measure earlier and with greater sensitivity the development and progression of mild cognitive impairment and Alzheimer's disease (AD). ADNI has reached its target enrollment of 800 participants, and supported development of a number of tools and methods now in use in the United States as well as in Japan, the European Union, and Australia. Other expansions

include a genome-wide association study of ADNI participants scheduled to provide the most extensive and robust dataset of its kind in the AD field; a study that allows for longitudinal analysis by the collection of additional cerebrospinal fluid from participants over several years; and a study exploring the use of PET and Pittsburgh Compound B (PIB) as a tool for developing biochemical markers. A recent ADNI study confirmed that certain changes in biomarker levels in cerebrospinal fluid may signal the onset of mild Alzheimer's and established a method and standard of testing for these biomarkers.

- For more information, see http://www.loni.ucla.edu/ADNI
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research*
- (E) (**NIA**, NIBIB)

Specialized Program of Translational Research in Acute Stroke (SPOTRIAS): The objective of the SPOTRIAS is to serve as an incubator for translational and early-phase clinical research studies. SPOTRIAS sites are located at medical centers where staff have the capacity to evaluate and treat stroke patients very rapidly after symptom onset. NIH supports eight SPOTRIAS sites that have made substantial progress, including impressive increases in tPA use; the establishment of three interlinked repositories for protein and DNA tissue samples, neuroimages, and clinical data; enrollment of more than 951 individuals with acute stroke into treatment protocols; the management of 20 early-phase clinical trials; and the training of 79 research fellows.

- For more information, see http://www.spotrias.com
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E, I) (**NINDS**)

NIH Establishes Neuro-Ophthalmology Clinical Research Network: The Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) Network was established in spring of 2009 to investigate disorders that bridge neurology and ophthalmology and that often are difficult to diagnose and treat. The Network involves more than 200 community and academic practitioners. This consortium will provide a unique opportunity to recruit and study hard-to-find patients to evaluate risks, diagnoses, and treatment options that could not be accomplished without a coordinated effort. The first clinical trial funded under this network will be the Idiopathic Intracranial Hypertension (IIH) Treatment Trial. IIH typically occurs in women of childbearing age. Obesity increases the risk 20-fold. IIH is characterized by an increase in intracranial pressure resulting in blurred vision, double vision, and permanent vision loss. This trial will compare the additional benefit of acetazolamide (a diuretic) added to a low-sodium, weight reduction diet in newly diagnosed patients. Future planned studies include comparing treatments for ocular manifestations in Graves' disease, an autoimmune disorder that causes hyperthyroidism, estimated to affect 2 percent of all women between the ages of 20 and 40. Patients with Graves' can develop protrusion of the eye balls and optic nerve damage. A network of researchers provides valuable expertise and widespread recruitment capabilities for studies of rare disorders.

- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (**NEI**)

Research on Rare Neurological Disorders: NIH supports research to uncover the causes of

and develop treatments for the hundreds of rare disorders that affect the nervous system, while also promoting research on topics such as stem cells, gene therapy, and neuroimaging that will impact multiple rare disorders. NIH reissued a Funding Opportunity Announcement (FOA) for new and renewal applications to continue the Rare Diseases Clinical Research Network (RDCRN), which funds collaborative clinical research consortia focused on rare diseases. NINDS will oversee the network's Data Management and Coordinating Center, and several of the consortia to be funded through this program focus on neurological disorders, including dystonia, brain vascular malformations, lysosomal storage disorders, and rare diseases of the autonomic nervous system. Through the NINDS translational research program, NIH supports milestone-driven therapy development for rare neurological diseases. Two funded projects, in Batten disease and Niemann-Pick disease, are nearing investigational new drug approval from FDA to conduct clinical trials, and a newly awarded project focuses on gene therapy approaches for the lysosomal storage disorders Tay-Sachs, San Fillipo, and Sandhoff disease. NIH also continues to support and encourage research to understand and treat Ataxia-telangiectasia and dystonia (including rare dystonias) through separate FOAs issued in collaboration with patient organizations.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-07-272.html
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-07-397.html
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-08-001.html
- For more information, see http://www.ninds.nih.gov/research/translational/Coop_Tran_Res.htm
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (**NINDS**, NCI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIAMS, NICHD, NIDCD, NIDCR, NIDDK, NIEHS, NINR, ODP/ORDR)

National NeuroAIDS Tissue Consortium: The National NeuroAIDS Tissue Consortium (NNTC) is a repository of brain tissue and fluids from highly characterized HIV-positive individuals. Established as a resource for the research community, the NNTC includes information from more than 2,280 participants in its clinical evaluation/tissue donation program, including nearly 750 brains, thousands of plasma and cerebrospinal fluid samples, and additional organs and nerves of interest.

- For more information, see http://www.hivbrainbanks.org/
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (E/I) (**NIMH**, NINDS)

Center for Neuroscience and Regenerative Medicine: The Center for Neuroscience and Regenerative Medicine (CNRM) is a collaborative initiative between NIH and the U.S. Department of Defense (DOD). The center's research mission is to discover methods to better intervene and prevent the long-term consequences resulting from traumatic brain injury (TBI). To increase research capabilities, the United States Congress established the CNRM as a collaborative intramural program and appropriated funds to the DOD for implementation. CNRM will study combat casualties cared for at Walter Reed Army Medical Center (WRAMC) and the National Naval Medical Center (NNMC) using advanced molecular and neuroimaging technology at the NIH CC. The CNRM seeks to serve as the catalyst for collaboration, innovation, and advancement of knowledge of the incidence of TBI and the identification of interdisciplinary approaches to assess TBI and promote recovery. CNRM research programs address the full spectrum of TBI, including the effect of high anxiety and the

concurrent development of post-traumatic stress disorder with TBI. In addition, the center will evaluate civilian patients with brain injury following trauma, to understand the relationship between military and civilian brain injury in patients as well as in preclinical models. CNRM research programs focus on (a) diagnostics and imaging, (b) biomarkers, (c) neuroprotection and models, (d) neuroregeneration, (e) neuroplasticity, and (f) rehabilitation and evaluation. The program leverages the strengths of NIH in neurosciences and neuroimaging together with DOD experience in brain trauma, neuroregeneration, and modeling.

- For more information, see http://www.usuhs.mil/cnrm
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (I) (**CC, NINR**, NIMH, NINDS)

Traumatic Brain Injury Program: Traumatic brain injury (TBI) presents enormous challenges because TBI affects so many people and can compromise virtually any human ability, depending on which parts of the brain are damaged. NIH research ranges from how TBI causes immediate and delayed damage to brain cells, to development of markers of damage, through large clinical trials to test interventions. Multicenter clinical trials now are testing hypothermia (cooling) in children and use of the hormone progesterone to minimize damage in adults. In addition, NIH launched a program to collect data on the use of multidrug combinations to better treat traumatic brain injury. Because the high rate of TBI among military personnel in Afghanistan and Iraq presents a special concern, a Federal Interagency TBI Research group now coordinates among NIH, VA, DOD, and other agencies. Trans-agency workshops have focused on TBI classification (Oct. 2007), combination therapies for TBI (Feb. 2008), opportunities and challenges of blast injury-induced TBI (April 2008), and "Integrated Research on Psychological Health and TBI: Common Data Elements" (March 2009). NIH is working with CDC on how to better track TBI in former military personnel and on evaluating the effectiveness of rehabilitation for TBI. The NINDS intramural research program has worked with the VA and DOD for many years on long-term neuropsychological outcomes of TBI in Vietnam veterans, and now in Iraq veterans. The NIH Intramural Research Program also is partnering now with the Uniformed Health Services University of the Health Sciences Center in the joint Center for Neuroscience and Regenerative Medicine, whose extensive TBI research programs range from molecular studies to understanding TBI mechanisms through rehabilitation and outcomes research.

- For more information, see http://www.ninds.nih.gov/news_and_events/proceedings/Neurological_Effects_of_Blast_Injury_Workshop.htm
- For more information, see http://www.ninds.nih.gov/news_and_events/proceedings/Combination_Therapies_for_Traumatic_Brain_Injury_Workshop.htm
- For more information, see http://www.ninds.nih.gov/news_and_events/proceedings/Classification_of_Traumatic_Brain_Injury_Workshop.htm
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-08-003.html
- For more information, see http://www.usuhs.mil/cnrm
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E, E/I) (**NINDS**, CC, NICHD, NIMH, NINR)

Epilepsy Research Benchmarks: In March 2007, more than 400 researchers, physicians, patients, family members, and voluntary organization leaders met on the NIH campus for the "Curing

Epilepsy 2007" conference. The meeting followed up on a successful White House-initiated conference held in 2000 that established the first set of Epilepsy Research Benchmarks to guide research directions. The epilepsy research community has made substantial progress since 2000, and attendees at the 2007 conference met to evaluate the original Benchmarks and discuss new directions. Participants voted on topic areas seen as most promising and in need of attention, and NIH solicited public input before the new Benchmarks were released in late 2007. The new Benchmarks for epilepsy research set short- and long-term goals related to preventing epilepsy and its progression; developing new therapeutic strategies and optimizing current approaches toward curing epilepsy; and preventing, limiting, and reversing comorbidities associated with epilepsy and its treatment. One such comorbidity is sudden unexplained or unexpected death in epilepsy (SUDEP). NIH convened a workshop in November 2008 focused on needs for research to understand and prevent SUDEP, and for improving awareness and education about SUDEP for patients, families, and health care providers. Adverse consequences also may be associated with epilepsy treatment, and NIH-supported researchers recently reported that valproate use during pregnancy, as compared to other common antiepileptic drugs, was associated with decreased IQ scores in 3-year old children. Understanding such risks may help patients and their physicians optimize care by allowing more informed choices among available treatment options.

- Kelley MS, et al. *Epilepsia* 2009;50(3):579-82. PMID: 19317887.
  Meador KJ, et al. *N Engl J Med* 2009;360(16):1597-605. PMID: 19369666.
  PMCID: PMC2737185.

- For more information, see
  http://www.ninds.nih.gov/funding/research/epilepsyweb/index.htm
- (E) (**NINDS**)

Other Notable Examples

High Resolution Anatomical and Functional Imaging of the Human Brain: NINDS and NIMH Intramural Research Programs are partnering to push the frontiers of MRI (magnetic resonance imaging) of the human brain and to make these developments available to researchers. The NINDS Laboratory of Functional and Molecular Imaging has led development of the next generation MRI device that uses a powerful 7T (Tesla) magnet, compared to the usual 1.5T magnetic strength. Overcoming the many technical challenges of imaging at 7T has yielded extraordinarily detailed images, which have contrast and spatial resolution as much as 100 times better than previous methods. These images reveal structures never before seen in the living human brain that may be critical in detecting early stages of disease. The NIMH functional MRI core facility serves more than 30 principal investigators on the NIH Bethesda campus and leads development of functional brain imaging. The facility has played a major role in making 3T MRI widely available for routine use. Together NINDS and NIMH investigators have pioneered imaging methods that increase the detail of structural and functional changes that investigators can detect in the brain, while improving time resolution and shortening duration for brain scans. A two-step strategy to continue this successful program will first translate 7T MRI from its present prototype design to routine use and then develop one of the world's first 11.7T MRI devices for imaging the human brain. Increased MRI resolution will improve diagnosis and monitoring of neurological and psychiatric disorders and open new opportunities for understanding brain function.

- For more information, see http://intramural.nimh.nih.gov/fmri/fmri_research.html
- This example also appears in Chapter 3: *Technology Development*
- (I) (**NINDS**, NIMH)

Lapsing During Sleep Deprivation is Associated with Distributed Changes in Brain Activation: Many serious accidents and medical errors result from lapses of attention that occur when sleep-deprived individuals fail to stay alert. Little is known about the neural correlates of attention lapses, but it appears they may be manifested as delayed or incorrect behavioral responses to certain stimuli. These attention lapses occur even after a normal night's sleep, becoming longer in duration and more frequent after sleep deprivation, suggesting that an underlying cause may be due to transient disruptions of cognitive control processes that rely on activation of the frontal lobes in the brain. To identify changes in task-associated brain activation associated with attention lapses, a group of NIH-supported researchers collected functional magnetic resonance images from healthy adults during a visual, selective attention task following sleep deprivation. The research findings reveal alterations in brain activity that occur as a result of sleep deprivation and the consequences of these changes to daily behaviors, including reduced abilities to maintain visual attention and process visual information. Understanding how the sleep-deprived brain impacts our ability to perceive and process information, as well as attend to everyday tasks, may lead to new discoveries that will address the underlying causes and symptoms of sleep deprivation.

- Chee MW, et al. *J Neurosci* 2008;28(21):5519-28. PMID: 18495886.
- For more information, see http://www.ncbi.nlm.nih.gov/pubmed/18495886
- (E) (**NINR**)

A Light Shines on Brain Circuits: NIH-funded researchers have devised an innovative method for modulating distinct brain circuits in the cortex. Calling their method "optogenetics," the researchers genetically engineered mouse neurons to be sensitive to fluorescent light in such a way that different colors of fluorescent light served as an on/off switch for the neurons. The researchers then were able to expose these mouse brain cells to specific kinds of fluorescent light to selectively block or enhance brain cell activity. They found that when they blocked the activity of a class of neurons, they eliminated a specific frequency range of circuit activity, whereas when they heightened activity of these cells, synchronized rhythm emerged. The combination of neuronal and synchronized rhythmic activities enhanced overall circuit function by boosting signal and reducing noise, making the messages transmitted between neurons loud and clear. The optogenetic approach presents a new and highly selective way of analyzing brain function, enabling researchers to determine the roles of different factors affecting brain performance and pathology.

- Sohal VS, et al. *Nature* 2009;459(7247):698-702. PMID: 19396159.
  Cardin JA, et al. *Nature* 2009;459(7247):663-7. PMID: 19396156.
- (E) (**NIMH**)

Clinical Research and Trials in Neurological Disease: NINDS funds more than 1,000 extramural clinical research studies. Clinical researchers are studying, for example, disease mechanisms, risk factors that contribute to health disparities, brain imaging, and genes that predispose to disease as well as conducting multisite clinical trials that test the safety and efficacy of new prevention strategies and treatments or compare existing interventions. In the past year, for example, an NICHD/NINDS clinical trial reported that a drug commonly used to delay labor can

prevent cerebral palsy in some circumstances, and a Veterans Administration/NINDS trial demonstrated that deep brain stimulation, a surgical intervention, is more effective than drug treatment at improving movement and quality of life for many people who have Parkinson's disease, but carries some risks. Among trials now underway, researchers are testing interventions to protect the brain following traumatic brain injury, to prevent stroke, to slow the progression of neurodegenerative diseases, and to treat multiple sclerosis. An independent study contracted by NINDS found that NINDS clinical trials which cost $335 million over 10 years provided benefits that exceeded $15 billion and added 470,000 healthy years of life to people in the United States. With guidance from an expert strategic planning panel, NINDS is continuing to improve the efficiency and payoff of the clinical trials program.

- Johnston SC, et al. *Lancet* 2006;367:1319-27. PMID: 16631910.
  Weaver FM, et al. *JAMA* 2009;301(1):63-73. PMID: 19126811.
  Rouse DJ, et al. *N Engl J Med* 2008;359(9):895-905. PMID: 18753646.
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (**NINDS**, NICHD)

Translational Research for Neurological Disorders: The Anticonvulsant Screening Program has catalyzed the development of six epilepsy drugs now on the market; the Neural Prosthesis Program has pioneered devices to restore lost nervous system functions; the Intramural Program has developed the first enzyme therapy for inherited disorders; and investigator-initiated research programs have led to development of FDA-approved drugs by industry. In 2003, NIH launched a program designed to expedite preclinical therapy development across all neurological disorders. The Cooperative Program in Translational Research supports academic and small business investigator-initiated projects in single laboratories or consortia, using milestone-driven funding and peer review tailored to the requirements of therapy development. Projects are developing drug, stem cell, or gene therapies for amyotrophic lateral sclerosis (ALS), Batten disease, epilepsy, Huntington's disease, muscular dystrophies, Parkinson's disease, tuberous sclerosis, and stroke, among other disorders. NIH also has developed several focused translational research initiatives over the last decade. The Spinal Muscular Atrophy (SMA) Project, for example, is an innovative pilot program to develop a treatment for SMA using a "virtual pharma" strategy that engages resources to carry out a drug development plan via contracts and collaboration. The project has two patents on compounds that show promise and is evaluating the safety of the most promising drug candidates, with the goal to begin human clinical trials as soon as possible. Translational research is a "signature project" for NINDS investment of American Recovery and Reinvestment Act funds.

- For more information, see http://www.ninds.nih.gov/funding/research/translational/index.htm.
- For more information, see http://www.ninds.nih.gov/research/asp/index.htm
- For more information, see http://www.ninds.nih.gov/research/translational/index.htm
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (**NINDS**) (ARRA)

Brain Tumor Research: NIH funds studies aimed at understanding the development and treatment of central nervous system and peripheral nervous system tumors, including medulloblastoma, neuroblastoma, and glioblastoma, as well as research on several inherited neurological tumor syndromes, including neurofibromatosis and tuberous sclerosis complex. In the past few years NIH has released a number of funding opportunity announcements (FOAs) related to

brain tumor research. A FOA on understanding and preventing brain tumor dispersal has been particularly effective in stimulating this area of research and has led to exciting advances. NIH also funds clinical studies investigating therapy delivery to the brain and evaluating the safety and tolerability of various therapies, including immunological therapies, vaccine therapy, monoclonal antibodies, and combination therapies. The Surgical and Molecular Neuro-Oncology Unit within the NIH Division of Intramural Research investigates basic mechanisms of brain tumor development and chemotherapy resistance to find new therapeutic strategies, particularly for malignant gliomas. NINDS and NCI co-lead the Trans-NIH Brain Tumor Working Group.

- For more information, see http://www.ninds.nih.gov/find_people/groups/brain_tumor_prg/index.htm
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAS-08-048.html
- This example also appears in Chapter 2: *Cancer*
- (E, I) (**NINDS**, NCI)

Peripheral Neuropathies: NIH funds studies focused on understanding the genetic basis and molecular and cellular mechanisms of many peripheral neuropathies, including diabetic neuropathy, HIV/AIDS-related and other infectious neuropathies, inherited neuropathies such as Charcot-Marie-Tooth, inflammatory neuropathies such as chronic inflammatory demyelinating polyneuropathy, and rare forms of peripheral neuropathy. Other notable projects include a natural history study of diabetic neuropathy, projects to improve the efficiency and effectiveness of diagnosis for various peripheral neuropathies, and a Phase III clinical trial to treat Familial Amyloidotic Polyneuropathy. In August 2008, a pair of program announcements was released to promote translational research in neuromuscular disease. Diseases included in these program announcements are those that affect the motor unit—the motoneuron, its process (axon), and the skeletal muscle fiber that is innervated by the neuron—such as peripheral neuropathy, amyotrophic lateral sclerosis, and muscular dystrophy. This unique structure-function framework provides a coordinated approach for therapeutic development in a subset of neurological diseases that share many common features, including the peripheral neuropathies.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-228.html
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-229.html
- This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
- (E) (**NINDS**, NIDDK)

From Genes to Therapy in Neurogenetic Disorders: Neurofibromatosis (NF) and tuberous sclerosis complex (TSC) are neurogenetic disorders that cause tumors on nerves, in the brain, and on other organs. Although the tumors are benign, consequences of their size and location can be serious. Clinical manifestations can include seizures, autism, and cognitive disability. NIH support led to identification of the genes underlying these disorders, and recently has enabled investigators to uncover disease mechanisms that point to strategies for therapeutic development. One NF study revealed that an NF1 gene mutation in bone marrow cells (which infiltrate peripheral nerves prior to NF tumor development) is necessary for tumor growth. Activation of c-kit, a molecule implicated in some cancers and targeted by the cancer drug Gleevec, enables release of the cells from bone marrow to stimulate neurofibroma growth. In this study, Gleevec treatment prevented formation and reduced neurofibroma size and activity. If clinical trials prove successful, Gleevec could become the first approved NF treatment. In TSC, genetic mutations cause deregulation of an anti-tumor molecule,

mTOR, which is a known target of rapamycin (a drug currently used to treat organ transplant rejection). In previous studies, rapamycin reduced the size of brain and kidney tumors in TSC patients. Recent NIH-supported research in mice revealed that rapamycin, via the mTOR pathway, inhibited TSC-induced brain enlargement and mortality, prevented seizures, and improved cognitive ability in mice, results which have led to clinical trials now in Phase III. Rapamycin also alleviated seizures in a rat model of epilepsy, which may shed light on TSC-associated neurological diseases, including autism and epilepsy.

- Ehninger D, et al. *Nat Med* 2008;14(8):843-8. PMID: 18568033. PMCID: PMC2664098.
  Meikle L, et al. *J Neurosci* 2008;28(21):5422-32. PMID: 18495876. PMCID: PMC2633923.
  Yang FC, et al. *Cell* 2008;135(3):437-48. PMID: 18984156. PMCID: PMC2788814.
  Zeng LH, et al. *J Neurosci* 2009;29(21):6964-72. PMID: 19474323. PMCID: PMC2727061.
  Zeng LH, et al. *Ann Neurol* 2008;63(4): 444-53. PMID: 18389497.
- This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- (E) (**NINDS**, NCI, NICHD, NIMH)

Know Stroke Efforts and New Stroke Slogan: In 2004, NIH entered a partnership with CDC to launch a grassroots education program called Know Stroke in the Community. The program was designed to identify and enlist the aid of community leaders who work as "Stroke Champions" to educate their communities about the signs and symptoms of stroke and the need for immediate action. The program focuses on reaching African Americans, Hispanics, and seniors in communities that have the health care systems in place to treat stroke. To date, the program has been implemented in 12 cities, educating 184 Stroke Champions who have conducted more than 600 community events. The program was expanded this year to Charleston, South Carolina, and, as a follow-up to that program, materials will be developed for coastal communities with unique dialects. NIH also recently expanded its public education programs by collaborating with the Brain Attack Coalition (BAC) to develop a new action-oriented message that all member organizations could use with their current stroke awareness efforts. The BAC is a group of organizations committed to stroke prevention and treatment chaired by NINDS. The new slogan—"Stroke strikes fast. You should too. Call 9-1-1."—was launched in May 2009 during Stroke Awareness Month.

- For more information, see http://stroke.nih.gov/about/
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
- (O) (**NINDS**)

Reducing Disparities in Stroke: NIH actively is engaged in a number of research projects designed to identify risk factors for stroke in minority populations and enhance prevention and treatment in these groups. The REasons for Geographic And Racial Differences in Stroke (REGARDS) Study is an observational study to explore the role of race and geographic differences on stroke risk factor prevalence and stroke incidence and mortality. Recruitment of the main REGARDS cohort was completed at the end of 2007 with 30,229 participants (41 percent African American and 59 percent white, 55 percent female and 45 percent male), and includes participants from 1,833 of the 3,111 counties (59 percent) in the 48 contiguous United States. The group already has published a number of important findings that partially explain why African Americans and residents of the southeastern "Stroke Belt" have higher risk of dying from stroke, and also findings documenting the consequences of not reporting stroke symptoms, including poor health outcomes and death. NIH also has established an acute stroke research and care center at the

Washington Hospital Center (WHC), a community hospital in Washington, DC, where more than 75 percent of stroke patients are African American or Hispanic. The center will collect data to aid in stroke prevention programs and will run two clinical trials, one on secondary stroke prevention and another on increasing tPA use among minorities. The program directly addresses GPRA goal: *By 2018, identify culturally appropriate, effective stroke prevention/intervention programs in minority communities*.

- Howard G, et al. *Prev Med* 2009;49(2-3):129-32. PMID: 19285103. PMCID: PMC2778033.
  Cushman M, et al. *Ann Neurol* 2008;64(5):507-13. PMID: 19067365. PMCID: PMC2802965.
  Howard G, et al. *Stroke* 2007;38(9):2446-52. PMID: 17673720.
  Wadley, G, et al. *Stroke* 2007;38:1143-1147. PMID: 17322077.
- For more information, see http://www.regardsstudy.org/index.htm
- This example also appears in Chapter 2: *Minority Health and Health Disparities*
- (E, I) (**NINDS**) (GPRA)

NIH Countermeasures Against Chemical Threats (CounterACT) Research Program: The CounterACT Research Network, as reflected in an NIH GPRA goal, develops medical countermeasures to prevent, diagnose, and treat conditions caused by chemical agents that might be used in a terrorist attack or released by industrial accidents or natural disaster. The Network, which has collaborated with the U.S. Department of Defense (DOD) from its inception in 2006, includes Research Centers of Excellence, individual research projects, small business research grants, contracts, and other programs that conduct basic, translational, and clinical research. One promising countermeasure, midazolam, which DOD researchers identified as a potential countermeasure against chemical agent-induced seizures, has entered clinical trials through the NIH Neurological Emergency Clinical Trials Network, and NIH is collaborating with DOD to complete animal studies necessary for its FDA approval as a nerve agent treatment. The New Drug Application is expected early FY 2010, with approval anticipated by the end of the year. The network also has developed six other lead compounds as therapeutics for cyanide, nerve agent, chlorine, and sulfur mustard, and has participated in pre-Investigational New Drug application meetings with FDA related to these efforts. One of the diagnostic devices developed by the program is being used in an NIH clinical trial. Three chemical agent therapeutics developed by the program also show promise as therapies for radiation exposures, and the program is collaborating with the NIH Medical Countermeasures Against Radiological and Nuclear Threats program.

- For more information, see
  http://www.ninds.nih.gov/research/counterterrorism/counterACT_home.htm
- For more information, see http://clinicaltrials.gov/ct2/show/NCT00809146
- For more information, see http://nett.umich.edu/nett/welcome
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Clinical and Translational Research*
- (E) (**NINDS**, NEI, NIAID, NIAMS, NICHD, NIEHS, NIGMS) (GPRA)

Acupuncture Shows Possible Effect for Tension Headaches: Millions of Americans suffer from chronic headaches. Tension headaches—characterized by pain/discomfort from tense/constricted muscles in the head, neck, or scalp—are a common form of headache. In most patients, tension headaches occur infrequently and can be treated with over-the-counter pain medicine. However, some people experience the headaches several days per month, even daily, and may benefit from other treatments. A review published by the Cochrane Collaboration looked at literature on acupuncture for tension headaches and analyzed findings from 11 randomized trials with

2,317 participants that compared acupuncture with a control or simulated acupuncture. The systematic review selected randomized trials with a post-randomization observation period of at least 8 weeks that compared clinical effects of an acupuncture intervention with a control (treatment of acute headaches only or routine care), a simulated acupuncture intervention, or another intervention in patients with episodic or chronic tension headache. The results of the literature review found that of the 11 studies: Two showed that patients who received acupuncture in addition to standard care had fewer headaches. Five found slightly better effects in patients who received true acupuncture compared with simulated acupuncture. Three of the four trials that compared acupuncture with physiotherapy, massage, or relaxation had methodological limitations. Their findings were difficult to interpret, but acupuncture appeared to have slightly better results than other therapies. The researchers concluded that acupuncture could be an option for patients suffering from frequent tension headaches.

- Linde K, et al. *Cochrane Database Syst Rev* 2009;(1):CD007587. PMID: 19160338.
- For more information, see http://nccam.nih.gov/research/results/spotlight/031709.htm
- (E) (**NCCAM**)

Comorbidity: Addiction and Other Mental Disorders: Drug addiction frequently is accompanied by other psychiatric diseases, which can complicate its diagnosis and treatment. Thus, NIH supports research on the multiple facets of psychiatric comorbidity across multiple health sectors. This approach explores whether drug use leads to mental illness or the reverse, what causes their frequent co-occurrence (e.g., shared genetic and environmental vulnerabilities or similarities in brain circuits and chemical messengers), and how to treat both comprehensively. Specific activities include epidemiological research on mental health/drug abuse comorbidity, such as secondary analyses of data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study and the National Comorbidity Survey to better understand the prevalence and variety of comorbidities, and clinical trials to help assess the actions of combined or dually effective behavioral and medication treatments (e.g., in adolescent and adult patients with attention deficit/hyperactivity disorder [ADHD] and substance abuse problems). It also includes a push for research to investigate drug abuse and mental health screening for all those entering the criminal justice system, a notable gap, particularly for adolescents. Another identified gap calls for research using preclinical models of comorbidity to explore the neurological bases of comorbid drug abuse and other mental illness (e.g., overlapping circuitry). Joint requests for applications issued by multiple ICs have elicited studies examining everything from the role of depression and anxiety in the tobacco epidemic to the neural bases of ADHD in fetal drug or alcohol exposure to improving care for co-occurring disorders in rural areas via new technologies. (Note: NESARC and the National Comorbidity Survey are nationally representative surveys in the United States that assess the prevalences and correlates of DSM-III-R disorders, including substance use and mental health disorders.)

- For more information, see http://www.drugabuse.gov/CTN/protocol/0028.html
- For more information, see http://www.drugabuse.gov/CTN/protocol/0029.html
- For more information, see http://www.nida.nih.gov/ResearchReports/comorbidity
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
- (E) (**NIDA**, NIAAA, NIMH)

NIH Strategic Plans Pertaining to Neuroscience and

Disorders of the Nervous System

National Institute of Neurological Disorders and Stroke (NINDS)

- *Neuroscience in the New Millennium*
- *Benchmarks for Epilepsy Research*
- *Report of the Stroke Progress Review Group*
- *The 2006 Parkinson's Disease Research Plan*

National Eye Institute (NEI)

- *National Eye Institute Strategic Planning*
- *National Plan for Eye and Vision Research* (2004)
- *Progress in Eye and Vision Research 1999-2006*
- *Ocular Epidemiology Strategic Planning Panel Report—Epidemiological Research: From Populations Through Interventions to Translation* (2007)
- *Age-Related Macular Degeneration Phenotype Consensus Meeting Report*
- *Pathophysiology of Ganglion Cell Death and Optic Nerve Degeneration Workshop Report*
- *Report of the Advances in Optical Imaging Symposium*

National Institute on Aging (NIA)

- *Living Long and Well in the 21st Century: Strategic Directions for Research on Aging*

National Institute on Deafness and Other Communication Disorders (NIDCD)

- *FY 2006-FY 2008 NIDCD Strategic Plan*
- *FY 2009-FY 2011 NIDCD Strategic Plan*

National Institute of Mental Health (NIMH)

- *The National Institute of Mental Health Strategic Plan*

National Institute on Drug Abuse (NIDA)

- *NIDA Five-Year Strategic Plan 2009*

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

- *National Institute on Alcohol Abuse and Alcoholism Five Year Strategic Plan FY 08-13*

Recommendations of the NIAAA Extramural Advisory Board (EAB)

- *Mechanisms of Alcohol Addiction*
- *Medications Development*

National Center for Complementary and Alternative Medicine (NCCAM)

- *Expanding Horizons of Health Care: Strategic Plan 2005-2009*

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

- *Neuroscience Research Support at NICHD*

Branch Reports to Council with Future Research Directions:

- *Child Development and Behavior Branch (CDBB), NICHD, Report to the NACHHD Council, January 2009*
- *National Center for Medical Rehabilitation Research (NCMRR), NICHD, Report to the NACHHD Council, January 2006*
- *Developmental Biology, Genetics, and Teratology Branch, Report to the NACHHD Council, September 2006*
- *Mental Retardation and Developmental Disabilities Branch, NICHD, Report to the NACHHD Council, June 2005*

Fogarty International Center (FIC)

- *Pathways to Global Health Research: Strategic Plan 2008-2012*

Office of AIDS Research (OAR)

- *FY 2008 Trans-NIH Plan for HIV-Related Research*
- *FY 2009 Trans-NIH Plan for HIV-Related Research*
- *FY 2010 Trans-NIH Plan for HIV-Related Research*

Other Trans-NIH Plans

- *Research Plan for Tuberous Sclerosis*
  (NCI, NHLBI, NIAMS, NICHD, NIDDK, NIMH, **NINDS, ORD**)
- *Muscular Dystrophy Research and Education Plan for the NIH*
  (**NINDS, NIAMS, NICHD** [co-leads])
- *Action Plan for the Muscular Dystrophies*
  (**NINDS, NIAMS, NICHD** [co-leads])
- *Report of the Brain Tumor Progress Review Group*
  (**NCI**, NINDS)
- *Research Plan for Ataxia-Telangiectasia*
  (NCI, NCRR, NEI, NHLBI, NHGRI, NIA, NIAID, NICHD, NIEHS, NIGMS, **NINDS**, ORD)
- *NIH Research Plan on Down Syndrome*
  (**NICHD**, NCI, NHLBI, NIA, NIAID, NIDA, NIDCD, NIDCR, NIMH, NINDS)
- *Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan*
  (CC, CSR, NCCAM, NCI, NCMHD, NCRR, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIBIB, NICHD, NIDA, NIDCD, NIDCR, **NIDDK**, NIEHS, NIGMS, NIMH, NINDS, NINR, NLM)
- *NIH Research Plan on Fragile X Syndrome and Associated Disorders*
  (**NICHD**, NIMH, NINDS, NIA, NIDDK, NIGMS, NCI, NIDCD)

Interagency Plans

- *2009 Strategic Plan for Autism Spectrum Disorder Research*

(**NIH** [**NIMH**, NICHD, NIEHS, NIDCD, NINDS])**,** *ACF, CMS, CDC, HRSA, SAMHSA, HHS Office on Disability, U.S. Department of Education)*